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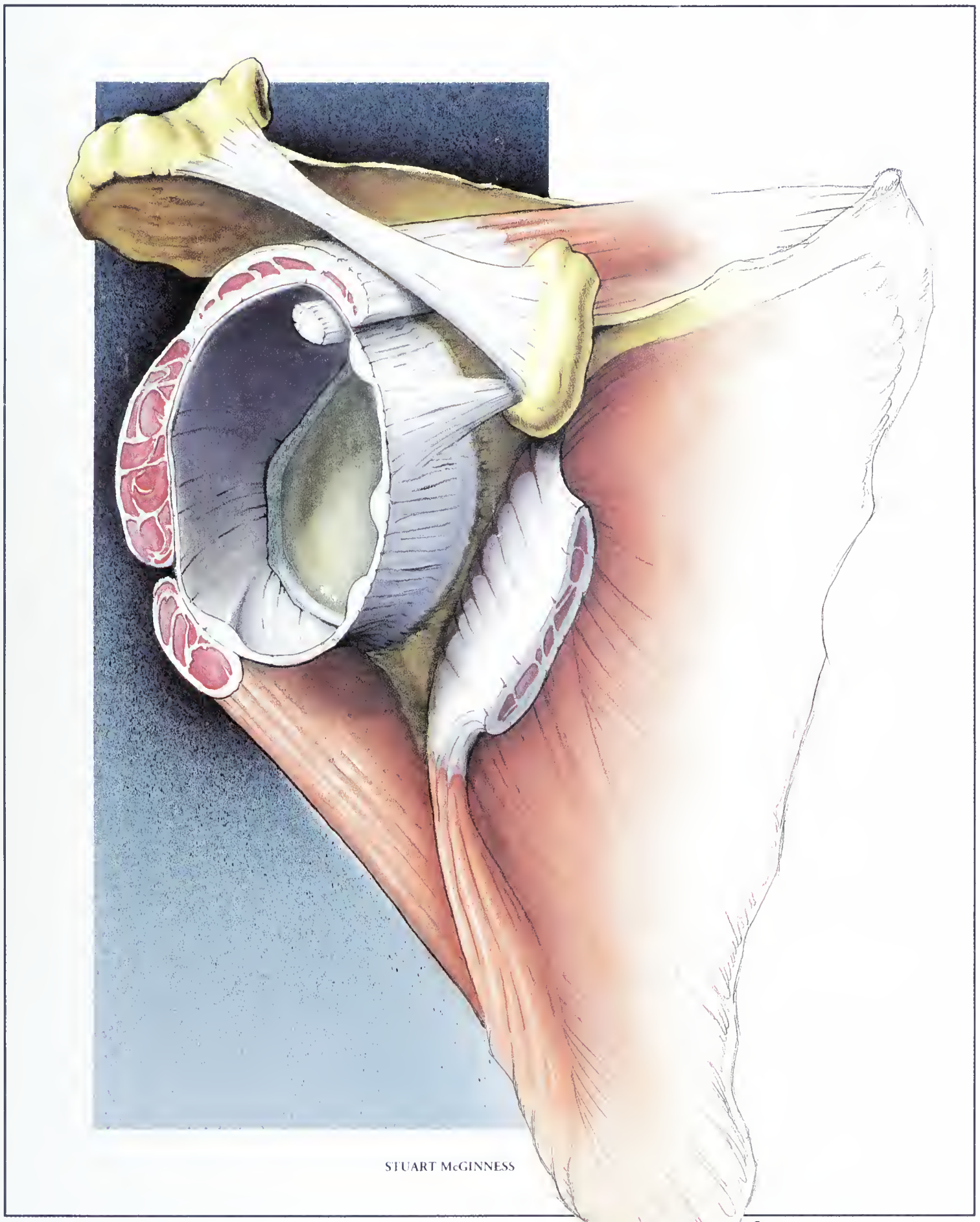

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- Cystic Fibrosis
- Shoulder Instability
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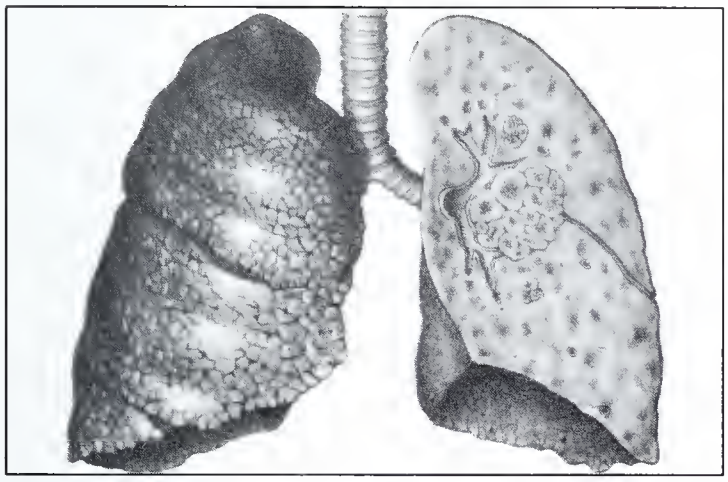

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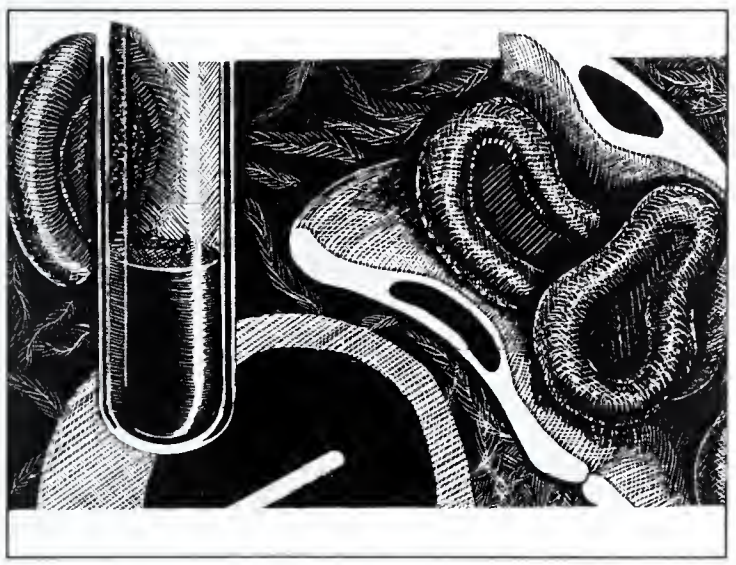

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Front cover illustration by Stuart McGinness, Department of Biomedical Communications, University of Toronto.

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Editorial

Dear Readers,

We are very pleased that the first issue of the 72nd edition of the University of Toronto Medical Journal was so well received. The Quick Diagnosis section with its new format, edited by Danyal Ibrahim, was especially exciting. However, even though we received a large number of responses for the $50 *Quick Diagnosis Competition*, no one provided the correct responses to all four of the cases. In this issue the Quick Diagnosis Competition is based on Emergency Rounds and includes a set of problems that we feel stress an important core of knowledge. One prize of $100 will be offered to the reader who provides the correct diagnosis for all of the problems.

The articles in this issue cover a broad range of topics from diverse fields of medicine, surgery and basic science. Our feature article which presents a review of current concepts on shoulder instability is the winning article for the R.I. Harris Undergraduate Award in Orthopaedic Surgery. Readers will also be interested in our other articles which include topics such as the molecular genetics of lung cancer, cystic fibrosis, extralobar pulmonary sequestration, genetic testing in the workplace and utilization of air ambulance in southern Ontario. In addition, our International Health Program article is a report from Egypt.

For those of you who were not able to attend the 1994 Gairdner Awards this past fall, we present in our *News and Views* section the profiles of the recipients of these awards.

Finally we are honoured to publish an exclusive interview with Dr Robert Buckman. This interview was conducted by Julian Harriss (9T7) and is combined with book reviews of Dr. Buckman's *How to Break Bad News* and *Magic or Medicine.*

We hope that our readers will enjoy this issue as much as the last.

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Shoulder Instability: Current Concepts

Joy Banerjee 9T7* and Paul H. Marks, MD, FRCSC**

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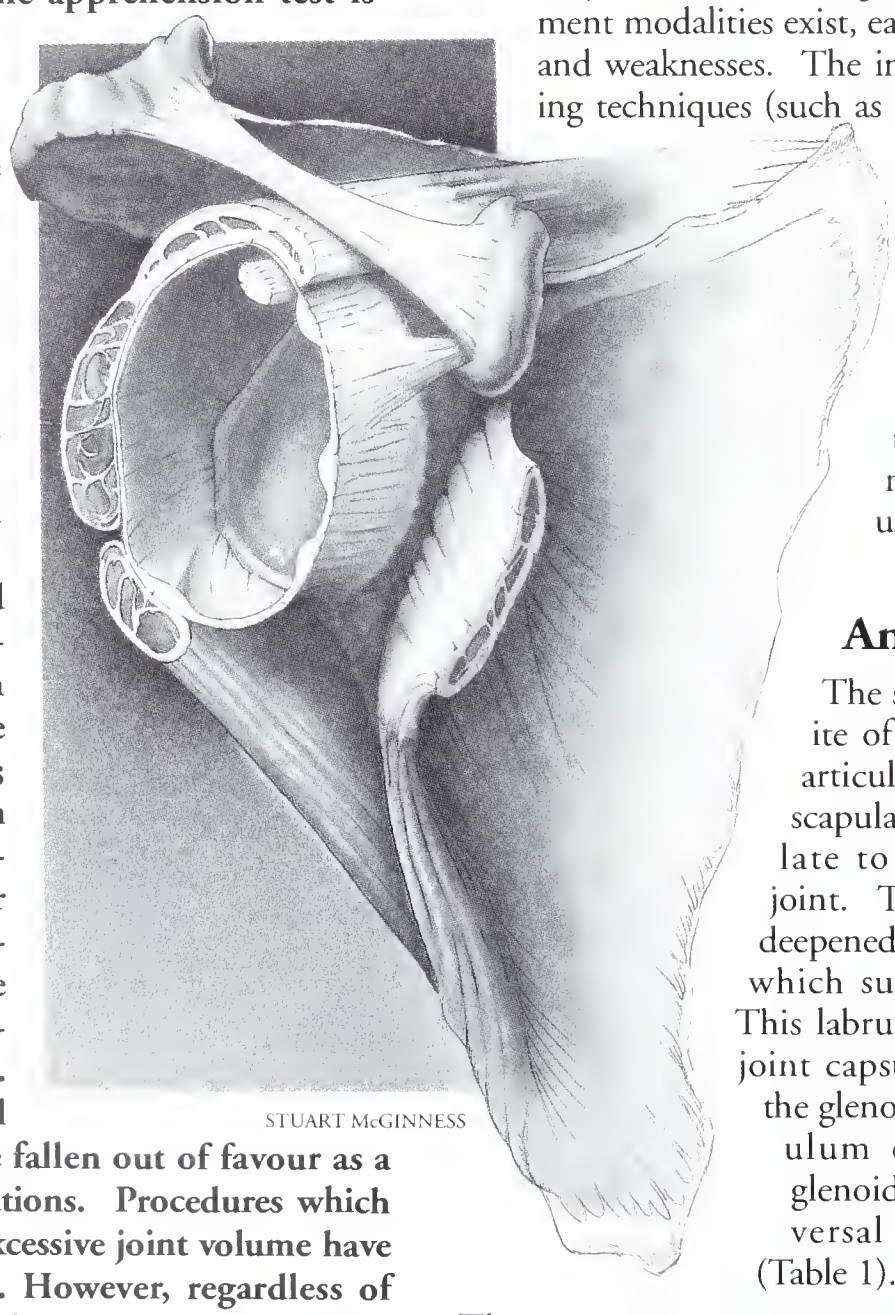
Abstract

Glenohumeral instability is a very common finding, especially in athletes. Accurate diagnosis relies on a thorough history and physical examination. One needs to ascertain the nature of onset, direction of instability and type of activities which aggravate the shoulder. On physical examination, the apprehension test is quite useful in cases of anterior instability, but is less so in posterior instability. Radiologic investigations include radiographs, computed tomography, arthrotomography and magnetic resonance imaging. Diagnostic accuracy, cost and waiting time are all issues that must be addressed when considering their use. Nonoperative treatment includes closed reduction followed by immobilization and an exercise regimen. No consensus has been reached with respect to the efficacy of the nonoperative treatment; however, there is a known documented high recurrence rate in the younger atraumatic anterior instability population. Operative treatment includes arthroscopic and open repair. Some of the more traditional open repair procedures have fallen out of favour as a result of long term complications. Procedures which address capsular laxity and excessive joint volume have yielded higher success rates. However, regardless of the procedure chosen, it has been a common finding that the throwing athlete has difficulty returning to his/her previous level of performance. Rehabilitative programs are aimed at returning full range of motion, strength and functional retraining.



STUART McGINNESS

Introduction

Glenohumeral instability is a common disorder, particularly in athletes[1,2]. Primarily suspended from the scapula by soft tissue and muscle, the humerus is provided with only minimal osseous support. Though this permits a greater range of motion, it also predisposes the joint to instability. Numerous diagnostic procedures and treatment modalities exist, each with their own strengths and weaknesses. The introduction of newer imaging techniques (such as computed tomography and magnetic resonance imaging) and arthroscopic surgery has improved the success of both evaluation and management of shoulder instability. The purpose of this paper is to explore the current strategies in diagnosis and treatment of the unstable shoulder.

Anatomy

The shoulder girdle is a composite of three joints and one bony articulation. The glenoid of the scapula and humeral head articulate to form the glenohumeral joint. The glenoid fossa is slightly deepened by a fibrocartilage labrum which surrounds the glenoid rim. This labrum is also connected to the joint capsule near its attachment to the glenoid. Unlike the deep acetabulum of the hip, the shallow glenoid fossa permits almost universal motion by the shoulder (Table 1).

The remaining two joints of the shoulder are the acromioclavicular and the sternoclavicular. The former is made up of the lateral end of the clavicle and the acromion process of the scapula. The latter is formed by the medial end of the clavicle and the manubrium sternum. Together, these two synovial joints augment the range of

Table 1

Active Movements of The Shoulder

1. Elevation through abduction (170-180 degrees).
2. Elevation through forward flexion (160-180 degrees).
3. Lateral rotation (80-90 degrees).
4. Medial rotation (60-100 degrees).
5. Extension (50-60 degrees).
6. Adduction (50-75 degrees).
7. Horizontal adduction/abduction (cross flexion/cross extension) (130 degrees).
8. Circumduction (200 degrees).

Table 2

History of The Unstable Shoulder

1. Onset of symptoms:	(i) gradual **or** (ii) initial traumatic event?
2. What was the position of the arm when injured?	
3. If there was a locked dislocation, was it self-reduced or did it require another person or physician[2]?	
4. Pain brought on by:	(i) violent activities such as throwing or (ii) simple tasks such as reaching overhead[8]?
5. Painful motions:	(i) anterior: abduction, external rotation, extension (ii) posterior: adduction, internal rotation, flexion[2]
6. Prior treatment:	(i) previous immobilizations (how long?) (ii) physical therapy (how effective?) (iii) previous surgery

motion of the shoulder by enabling the humerus to move through a full 180° of motion. The scapulothoracic articulation is formed by the anterior aspect of the scapula and the posterior thoracic cage, though the subscapularis muscle actually separates the two. This articulation is involved in elevation, depression and upward and downward rotation of the shoulder.

Covering the glenohumeral joint are the rotator cuff tendons: the supraspinatus along the superior aspect, the infraspinatus and the teres minor along the posterior aspect and the subscapularis along the anterior aspect.

Classification

Glenohumeral instability can be assessed using a number of criteria. Chief among them are degree and direction. With respect to the former, instability can be described as a continuum extending from subluxation (increased glenohumeral translation) to frank dislocation. It should be noted that one does not necessarily develop into the other[3]. Primary and recurrent dislocation is most common among those between the ages of 20 and 30 years[4]. Older patients who suffer dislocations are more prone to associated tears of the rotator cuff tendons[5]. This may be a result of wear and degeneration[6]. Historically, attention has focused on anterior instability since it has been estimated that 95% of shoulder instability is in this direction. Recently, however, there has been an increased interest in posterior and multidirectional instability (MDI)[2]. The latter can often present with a similar history to anterior instability. However, the presence of a sulcus sign (increased gap below the acromion) is indicative of MDI. Instability can also be categorized as to whether there was a traumatic episode leading to subluxation or dislocation. A distinction is also made between voluntary and involuntary instability. The former represent an intriguing group which may further be differentiated on the basis of whether or not the patient suffers from a psychiatric disorder. In both cases, dislocation is achieved by voluntary muscular contraction[7].

Evaluation

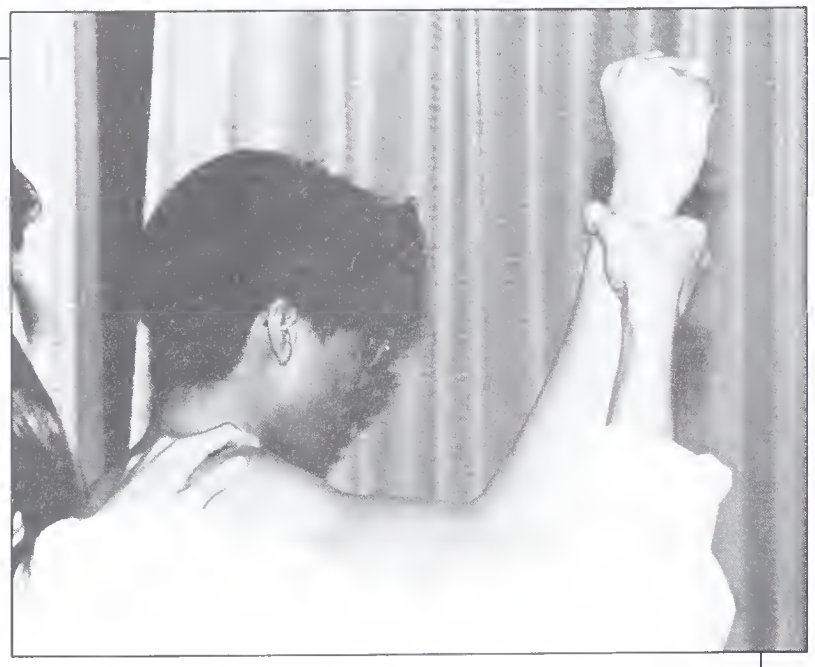
History

A thorough history is essential in the accurate diagnosis of shoulder instability (Table 2). One must determine whether the onset of symptoms was

Table 3

Physical Examination Procedures

1. All examination techniques should be performed bilaterally.
2. The patient's shoulder muscles should be relaxed during the exam[9].
3. Evaluate joint hyperextension to assess any possible predisposition to instability[3].
4. Note any muscle wasting on the affected side (deltoid, supraspinatus, infraspinatus).
5. Tenderness of the anterior joint space may indicate anterior instability or impingement syndrome[2].
6. Tenderness of the posterior joint space is found in two-thirds of patients with posterior instability[2] and in some patients with anterior instability[8].
7. A positive sulcus test is often seen with multidirectional instability[10]. Repeat the test with the arm abducted 90 degrees and apply a downward force[2].
8. The apprehension[10] and anterior drawer tests are useful in diagnosis of anterior instability
9. The posterior drawer test can help in the diagnosis of posterior instability[10].
10. A posterior dislocation may be demonstrated in a patient who is unable to turn his/her palm of affected side when both arms are extended (along with a negative anteroposterior radiograph and no response to therapy)[11].



a

b

Figure 1: The Apprehension Test.

(a) The arm is flexed 90° at the elbow and

(b) progressively externally rotated while applying intermittent anterior forces. Subjective apprehension is considered a positive test.

gradual or if there was an initial traumatic episode. Knowing the position of the affected arm at the time of injury can be helpful. If there was a locked dislocation, was it self-reduced or did the reduction require another person or physician[2]?

Note which activities and positions cause discomfort. Some patients may experience pain only during violent activities such as throwing, while others are unable to carry out simple tasks such as reaching overhead without discomfort[8]. Anterior instability often presents with pain or apprehension during abduction, external rotation and extension[2]. Moreover, while anterior pain may be expected, it is not uncommon to note posterior pain as well[8]. Discomfort resulting from posterior instability is often associated with flexion, adduction and internal rotation.

A list of all prior treatment should be compiled. Had the shoulder ever been immobilized? If so, for what length of time? What sort of physiotherapy program, if any had been pursued? Finally, establish whether or not surgery had been performed to correct the instability.

Physical Exam

Along with the history, a careful physical exam can aid in the diagnosis of instability (Table 3). Bilateral examination of the shoulders provides a comparison between the affected side and normal shoulder. The shoulder muscles should be relaxed to prevent intrinsic stabilization of the

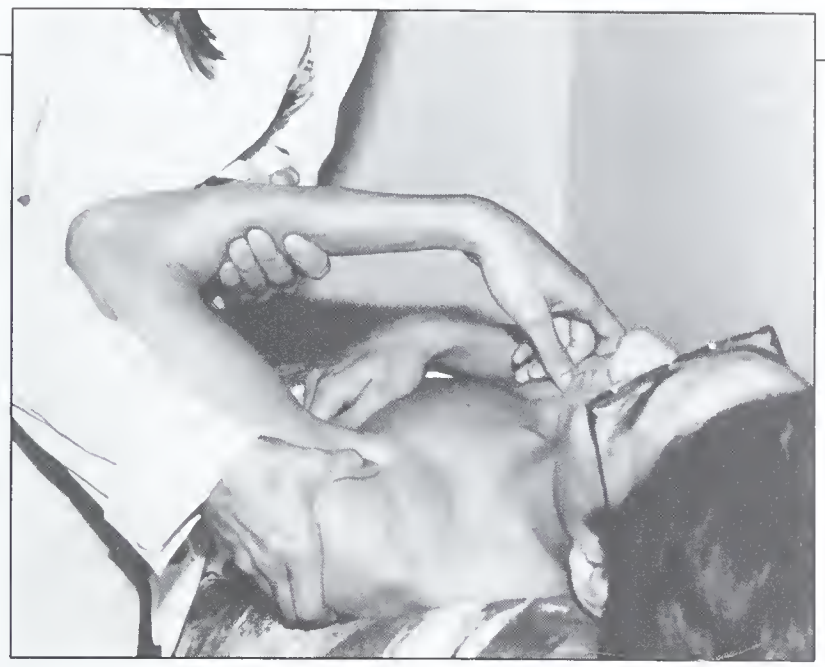
a

b

Figure 2: The Anterior Drawer Test.

(a) With the patient's arm tucked in the examiner's axilla,

(b) the humerus can be levered forward while stabilizing the scapula.



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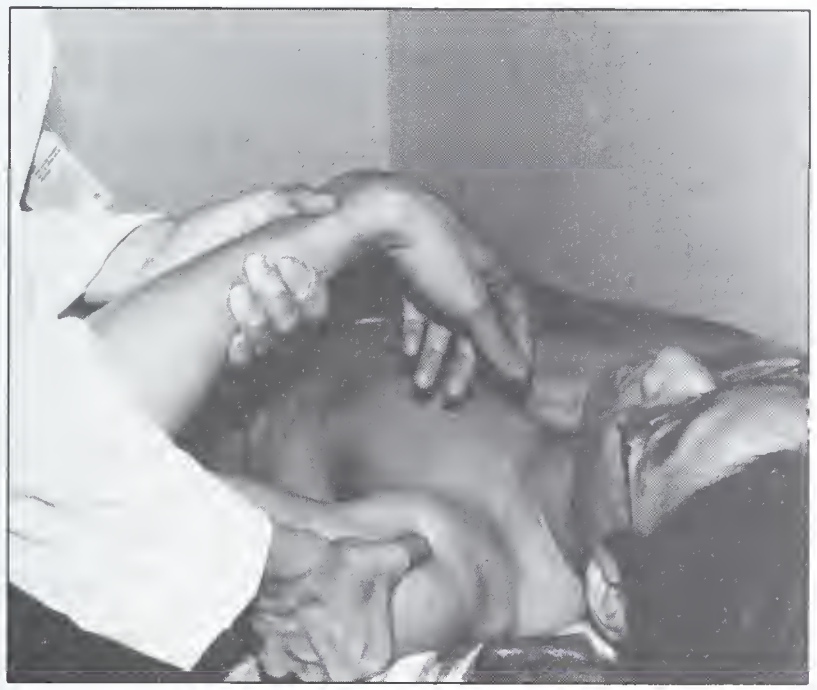

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Figure 3: The Posterior Drawer Test.

(a) With the patient's elbow flexed to 120° the examiner stabilizes the scapula and

(b) uses her thumb to apply posterior forces to the humeral head at 80° to 120° of abduction.

joint during the exam[9]. It has been suggested that loose-jointed athletes may be at increased risk for glenohumeral instability[3]. Testing for hyperextension of the elbows, knees and metacarpophalangeal joints provides an indication for generalized joint laxity.

Inspection of both shoulders may reveal wasting of the deltoid, supraspinatus and infraspinatus muscles on the affected side. Occasionally, winging of the scapula may accompany posterior instability. Tenderness on palpation of the anterior joint space is common with anterior instability, but can also present in shoulders with impingement syndrome[2]. Palpation of the posterior joint space has been reported to elicit pain in two thirds of patients with posterior instability[2].

Inferior instability is almost always associated with multidirectional instability[10] and can be assessed by performing the sulcus test. The patient's humerus is pulled downward while in the neutral position. The test is then repeated with the arm abducted 90°, and a downward force applied to the proximal humerus[2].

The apprehension test is useful in the diagnosis of anterior instability (Figure 1). Lateral rotation of the humerus at 45°, 90° and 135° of abduction combined with intermittent anterior forces at the humeral head provokes anterior subluxation. Subjective apprehension by the patient is interpreted as a positive test[10]. The anterior drawer test helps diagnosis of instability in the same direction (Figure 2). With the patient supine and his hand tucked in the examiner's axilla of the opposite side, the examiner stabilizes the scapula with one hand (same side as being examined) while using the other to lever the patient's arm forward into subluxation.

Gerber and Ganz[11] have suggested that the low incidence of posterior instability may be due in part to the absence of a test which identifies with certainty subluxation in this direction. One test used to assess possible posterior instability is the posterior drawer test (Figure 3). While supine, the examiner grasps the patient's proximal forearm (with his hand of the same side) and flexes the elbow to 120°. The examiner then stabilizes the scapula with his hand of the opposite side by placing his index and middle fingers along the scapular spine. Positioned immediately lateral to the coracoid process the thumb can be used to apply posterior forces to the humeral head. This test is performed while the shoulder is progressively abducted from 80° to 120°[10].

In patients whose anteroposterior radiograph is negative and who showed no response to conservative treatment, a posterior dislocation could be demonstrated by the inability of the patient to turn his palm up on the affected side when his arms were extended[11].

Radiologic Investigations

Various radiologic modalities can assist in diagnosing glenohumeral instability. Some of the more common radiographic views ordered are: anteroposterior, lateral, axillary and the scapular plane view. Changes in the humeral head and glenoid are commonly seen following traumatic instability[12]. Rowe and Zarins noted that the lesions responsible for anterior dislocation were easily spotted in the anteroposterior view. However, radiographs in the same view of posterior dislocations often were interpreted as negative[11]. Another common finding is posterolateral impression defects on anteroposterior views (with internal rotation) following traumatic episodes[2].

Also diagnostically useful, but more expensive are computed tomography (CT) and arthrotomography (arthro-CT) as well as magnetic resonance imaging (MRI). While CT scans provide information relating to the bony architecture, arthro-CT allows evaluation of the labrum

and capsular volume[13]. MRIs are useful in cases of pathology (Figure 4) involving the anterior labrum but less so in instances involving the posteroinferior labrum[14,15]. Moreover, its cost and waiting list serve as a deterrent to its frequent use.

Figure 4: Magnetic Resonance Image of the shoulder demonstrating enthesopathy (damage to the musculotendinous attachment to the bone)

Examination Under Anaesthesia

Before any operative procedure is performed, an examination under anaesthesia must be conducted to confirm the diagnosis. Because the shoulder muscles are relaxed, the direction and degree of instability can be assessed[2].

Anterior, posterior and inferior translation of the humeral head within the glenoid can be determined by performing a drawer test. With the arm abducted 90°, anterior and posterior translation is graded as being +1 (humeral head translated to the rim of glenoid without slipping out of it), +2 (humeral head dislocates from glenoid, but spontaneously reduces upon release of pressure) and +3 (frank glenohumeral dislocation without spontaneous reduction upon release of pressure)[16].

Manipulation should be performed bilaterally[17] and begin with the humeral head centred in the glenoid. Otherwise, it is possible to interpret an anterior subluxation returning to a reduced position as a reduced shoulder posteriorly subluxating[2].

Nonoperative Treatment

Conservative, nonoperative modalities are usually first implemented to treat shoulder instability. The treatment plan for a dislocated shoulder begins with a closed reduction, followed by a period of immobilization and finally, a rehabilitative exercise program. The aim of such a regimen is to strengthen the surrounding muscles and thereby provide better support for the shoulder. A program with increasingly resistive exercises will achieve such a goal[2]. Davis found that 75% of patients with recurrent dislocation responded well to exercises[18], while Yoneda reported that, following an anterior dislocation, 82.7% of patients expressed satisfaction with an exercise program for the shoulder[19]. It has been suggested that, in cases of anterior instability, certain movements be avoided and an external check rein of tape or abduction harness should be considered to augment the exercise program[1]. In cases of voluntary dislocation, a closely supervised program designed to provide resistance to internal and external rotation is usually quite successful. However, if there is no improvement and the patient demonstrates emotional or personality difficulties, a psychiatric consultation should be arranged[7]. Though no treatment may be considered a form of treatment in itself, May noted that spontaneous recovery from recurrent dislocation is impossible[20].

The success of nonoperative treatment in cases of subluxation vary. One study reported good to excellent results in 80% of patients with a multidirectional atraumatic subluxation compared with only 16% in cases of multidirectional subluxation of a traumatic nature[12]. However, Burkhead and Rockwood noted uniformly poor results in their study of patients with traumatic subluxation. Only 18% of those with and 9% without previous dislocation reported good or excellent results with an exercise regimen[12].

With respect to immobilization, both Hovelius[21] and Simonet and Cofield[22] found no correlation between length of immobilization and rate of recurrence of instability. Rowe reported similar findings in his study of nearly 500 shoulders[4].

Though some feel that muscle strengthening programs can not hope to truly compensate for instability, an exercise regimen is of use even if surgery is chosen. If the patient receives no relief following physical therapy, it is clear to that person that every conservative approach short of an operation has been pursued. Moreover, it allows the surgeon to become better acquainted with the patient's motivation and expectations[8]. These are key factors in selecting patients for operative treatment.

Operative Treatment

Arthroscopy

At the present time, the role arthroscopic surgery on the unstable shoulder is to allow identification of any intra-articular pathology. In conjunction with the history, physical exam and examination under anaesthesia, it provides useful diagnostic information.

Ideally, arthroscopic debridement of "capsular fronds" resulting from a labral tear result in decreased inflammation with a concomitant reduction in pain for the individual. As a result, the patient is better able to tolerate a rehabilitative exercise regimen[2]. However, it should be noted that debridement does not correct any labral

pathology associated with instability. To date, short term results have been promising, though some studies show that improvements deteriorate with time[2,23].

Arthroscopic techniques for shoulder stabilization are now being used more frequently. An anterior labral dissociation from the glenoid (Bankart lesion) can be repaired using staples, removable rivets, sutures and bioabsorbable tacks (Figure 5). Short term follow ups results have revealed success rates of up to 97%[24] while other studies indicate that arthroscopic staple capsulorrhaphy has the highest rates of complication with 5.3%[25]. Pitfalls of this technique usually stem from incorrect placement or loosening of the staple[26].

Because this style of repair causes far less damage to anterior soft tissue structures, it is felt that a better functional outcome is likely. Warner and Marks remarked that this was especially important in young throwing athletes who require full external rotation and power[16]. This method of repair has also been recommended for patients who have declined open stabilization or who have previously undergone an unsuccessful open procedure[26].

Open Repair

Considering that 95% of all instability is of the anterior variety[16], it is not surprising that there are numerous procedures which address this type of instability[26]. Protzman mentioned two main indications for anterior shoulder repair. First, instability must occur during performance of daily activities or required overhead tasks. Second, the patient should be motivated and have realistic goals regarding results following the surgery[8]. Overall, the rate of redislocation following one of the more common procedures is approximately 3%[2]. However, there are limitations and complications associated with all techniques.

In a Bankart repair, attachment of a dissociated glenoid labrum is done with sutures. While some studies have shown very favourable results[27,28], care must be taken not to incise the capsule too far laterally. This can occur if the arm is internally rotated, thereby allowing the redundant capsular tissue to fold over itself. When the capsule is reattached to the glenoid, an excessively tight joint capsule results. Limited external rotation is often the consequence[16]. Preparation of the osseous holes through which the sutures are passed must be done with appropriate visualization of the surrounding area. If the holes are too close to the rim of the glenoid, a fracture may result[2].

Figure 5: A bioabsorbable device is shown being implanted arthroscopically to repair a Bankart (anterior labral lesion) tear.

Using staple fixation for labral detachments (du Toit procedure) allow the patient to begin therapy soon after the operation[9] but complications arising from the metal hardware make the procedure less favourable.

Procedures like the Magnuson-Stack and Putti-Platt which transpose and shorten the subscapularis, respectively to stabilize the shoulder have fallen into disfavour because of decreased external rotation and possible development of arthritis arising from excessive tightening[16].

Techniques which transplant the coracoid to the scapular neck to serve as a bone block barrier to further dislocation have several drawbacks. Placement of the bone block too far medially will result in anterior subluxation while placement too far laterally will restrict the movement of the humeral head within the glenoid[16]. Moreover, damage to the musculocutaneous nerve has been reported with this procedure[29]. As well, complications arising from the metal hardware, namely the screw are not uncommon[26].

Osteotomies of the proximal humerus (Weber) or glenoid (Meyer-Burgdorff) have fallen out of favour since radiologic evidence has shown normal glenohumeral anatomy in most unstable shoulders[30,31].

Capsulorraphy procedures which address capsular laxity and excessive joint volume which do not shorten the subscapularis muscle have allowed a higher percentage of patients return to full activity levels[32,33,34].

A retrospective study of various anterior stabilizing techniques found that 67% of all patients suffered instability post operatively[1]. Furthermore, is was reported that most surgical repairs for shoulder dislocation resulted in limited lateral rotation.

Posterior labral detachment, capsular laxity and abnormalities of the glenoid have all been suspected of the underlying pathology of posterior instability. Unfortunately, most of the operative procedures aimed at providing bony stabilization have not been proven to address the underlying pathology[3]. Indeed, osteotomies have been prone to intra-articular extension as well as being responsible for conversion to anterior instability[3]. However, there has been reported success with

capsulorraphies (with or without a bone block) which attempted to correct excessive posterior joint laxity and associated posterior labral damage[2,3].

Multi-directional instability (MDI) is often characterized by pain, instability and, more infrequently, parasthesias[35]. Many failed anterior repairs were later diagnosed as MDI[36].

Unlike classic anterior instability, multi-directional instability may not be caused by trauma[35]. Cooper and Brens reported that 76% of patients in their study did not suffer dislocations as a result of a traumatic episode[36].

Laxity is a common operative finding in patients. Altchek et al. found that all 42 individuals in their study exhibited capsular laxity[37], while Cooper and Brems reported a 90% incidence[36].

Neer and Foster explained that a unidirectional approach to MDI usually fails because inferior capsular laxity is not addressed[35]. They found that they were able to circumvent this dilemma by performing an inferior capsular shift using either an anterior or posterior approach[35].

It was recommended that this approach be considered for those patients who were unresponsive to non-operative treatment and anti-inflammatory medication[35]. Short term follow up by Neer and Foster revealed a 97% satisfaction rate among patients on whom the procedure was performed, while Cooper and Brems reported a success rate of 91%.

As a general comment regarding surgical intervention for shoulder instability, it has been noted that throwing athletes are often unable to return to their level of performance before the operation[38]. Moreover, patients with voluntary dislocation in conjunction with a psychiatric problem do not respond well to any mode of treatment, including surgery[7].

Rehabilitation

Following an operative procedure and period of immobilization, a rehabilitative program is designed for the patient. The basic goals are to prevent recurrence and a return to full activity. The program should aim to strengthen shoulder muscles as well as increase range of motion[2]. Pollock and Bigliani noted that the length of immobilization and style of program depends on the direction of instability, quality of tissue, type of repair and requirements of the patient. They also advocated protecting patients with multidirectional instability or who had been treated with a posterior capsulorraphy longer than those who had had a procedure for anterior instability. Patients having been treated for anterior instability began exercises in the third week, those treated for MDI or with posterior capsulorraphy do not begin their therapy until several weeks later. In both cases, return to full activity in sports does occur until up to 12 months postoperatively.

Summary

Glenohumeral instability is common disorder which encompasses a number of conditions. Though increasingly sophisticated imaging devices are becoming available, a detailed history and careful physical exam are the most important tools for the clinician when making a diagnosis.

Treatment can either come in the form of conservative exercise or surgical intervention. The former is often the first modality employed and is used to strengthen the shoulder musculature in hopes of at least partially alleviating the glenohumeral instability. Even if surgery is the treatment of choice, an initial period of therapy may be prescribed for the patient. Operative treatment includes arthroscopy and open repair. Though mostly used for debridement, the arthroscope is increasingly being used for repair of the underlying pathology. Rehabilitative programs follow operations to maximize the benefit of the surgery. Regardless of the treatment employed, a full recovery and return to activities is the ultimate goal.

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References

1. Hawkins RH, Hawkins RJ. Failed Anterior Reconstruction For Shoulder Instability. J Bone Joint Surg 1985; 67B: 709-14.
2. Pollock RG, Bigliani LU. Glenohumeral Instability: Evaluation and Treatment. J Am Acad Orthop Surg 1993; 1:24- 31.
3. Fronek J, Warren Rf, Bowen M. Posterior subluxation of the glenohumeral joint. J Bone Joint Surg 1989; 71A: 205-16.
4. Rowe CR. Prognosis in dislocation of the shoulder. J Bone Joint Surg 1956; 38A: 957-77.
5. Hawkins RJ, Bell RH, Hawkins RH, Koppert GJ. Anterior dislocation of the shoulder in the older patient. Clin Orthop 1986; 206: 192-5.
6. Craig EV. The posterior mechanism of acute anterior shoulder dislocations. Clin Orthop 1984; 190: 212-6.
7. Warner JJP, Marks PH. Management of complications of surgery for anterior shoulder instability. Sports Med Arth Review 1993; 1: 272-92.
8. Rowe CR, Pierce DS, Clark JG. Voluntary dislocation of the shoulder. A preliminary report on a clinical electromyographic and psychiatric study of twenty-six patients. J Bone Joint Surg 1973; 55A: 445-60.
9. Protzman RR. Anterior instability of the shoulder. J Bone Joint Surg 1980; 62A: 909-18.
10. Sisk TD, Boyd HB. Management of recurrent anterior dislocation of the shoulder: duToit-type or staple capsulorrhaphy. Clin Orthop 1974; 103: 150-6.
11. Gerber C, Ganz R. Clinical assessment of instability of the shoulder: with special reference to anterior and posterior drawer tests. J Bone Joint Surg 1984; 66B: 551-6.
12. Rowe CR, Zarins B, Ciullo JV. Recurrent transient subluxation of the shoulder after surgical repair. J Bone Joint Surg 1984; 66A: 159-68.
13. Burkhead WZ, Rockwood CA Jr. Treatment of instability of the shoulder with an exercise program. J Bone Joint Surg 1992; 74A: 890-6.
14. Singson RD, Feldman F, Bigliani LU. CT arthrographic patterns in recurrent glenohumeral instability. AJR 1987; 149: 749-53.

15. Iannotti JP, Zlatkin MB, Esterhai JL, et al. Magnetic resonance imaging of the shoulder: Sensitivity, specificity, and predictive value: J Bone Joint Surg 1991; 73A: 17-29.
16. Legan JM, Burkhead TK, Goff WB II, et al. Tears of the glenoid labrum: MR imaging of 88 arthroscopically confirmed cases. Radiology 1991; 179: 241-6.
17. Rowe CR, Sakellarides HT. Factors related to recurrences of anterior dislocation of the shoulder. Clin Orthop 1961; 20: 40-7.
18. Davis, A.G. A conservative treatment for habitual dislocations of the shoulder. J Am Med Assn 1936; 107: 1012-1015.
19. Yoneda B, Welsh RP, MacIntosh DL. Conservative treatment of shoulder dislocation in young males. In Proceedings of The Canadian Orthopaedic Association. J Bone Joint Surg 1982; 64B: 254-5.
20. May VR. A modified Bristow operation for anterior recurrent dislocation of the shoulder. J Bone Joint Surg 1970; 52A:1 010-6.
21. Hovelius L. Anterior dislocation of the shoulder in teenagers and young adults: five year prognosis. J Bone Joint Surg 1987; 69A: 393-9.
22. Simonet WT, Cofield RH. Prognosis in anterior shoulder dislocation. Am J Sports Med 1984; 12: 19-23.
23. Alchek DW, Skyhar MJ, Warren RF. Shoulder arthroscopy for shoulder instability. Instr Course Lect 1989; 38: 187-98.
24. Johnson LL. Arthroscopic management for shoulder instability: stapling, presented at Arthroscopy Association of North America Specialty Day, Atlanta February,1988.
25. Neer CS, Foster CR. Inferior capsular shift for involuntary inferior and multidirectional instability of the shoulder. J Bone Joint Surg 1980; 62A: 897-908.
26. Wiley AM. Arthroscopy for shoulder instability and using a technique for arthroscopic repair. Arthroscopy 1988; 4: 25-30.
27. Rowe CR, Patel D, Southmayd WW. The Bankart procedure: A long-term end-result study. J Bone Joint Surg 1978; 60A: 1-16.
28. Thomas SC, Matsen FA III. An approach to the repair of avulsion of the glenohumeral ligaments in the management of traumatic anterior glenohumeral instability. J Bone Joint Surg 1989; 71A: 506-13.
29. Cameron JC, Hall M, Courtney BC. The Bristow procedure for recurrent anterior dislocation of the shoulder. J Bone Joint Surg 1985; 67B: 327.
30. Randelli M, Gambrioli PL. Glenohumeral osteometry by computed tomography in normal and unstable shoulders. Clin Orthop 1986; 208: 151-6.
31. Cyprien J, Vasey HM, Burdet A, et al. Humeral retroversion and glenohumeral relationship in the normal shoulder and in recurrent anterior dislocation (scapulometry). Clin Orthop 1983; 175: 8-17.
32. Alchek DW, Warren RF, Skyhar MD, et al. T-plasty modifcation of the Bankart procedure for multidirectional instability of the anterior and inferior types. J Bone Joint Surg 1991; 73A: 105-12.
33. Jobe FW, Giangarra CE, Kvitne RS, et al. Anterior capsulolabral reconstruction of the athlete in overhand sports. Am J Sports Med 1991; 19: 429-34.
34. Bigliani LU, Kurzweil PR, Schwartzbach CC, et al. Inferior capsular shift procedure for anterior/inferior shoulder instability in athletes. Orthop Trans 1989; 13: 560.
35. Neer CS. Shoulder Reconstruction, p. 288. Philadelphia, W.B. Saunders, 1990.
36. Cooper RA, Brems JJ. The inferior capsular shift for multi-directional instability of the shoulder. J Bone Joint Surg 1992; 74A: 1516-21.
37. Altchek DW, Warren RF, Skyhar MJ, Ortiz G. T-plasty anterior repair for anterior and inferior instability of the shoulder. J Bone Joint Surg 1991; 73A: 105-11.
38. Torg JS, Balduini FC, Bonci C, Lehman RC et al. A modified Bristow-Helfet-May procedure for recurrent dislocation and subluxation of the shoulder. J Bone Joint Surg 1987; 69A: 904-13.

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The Molecular Genetics of Lung Cancer

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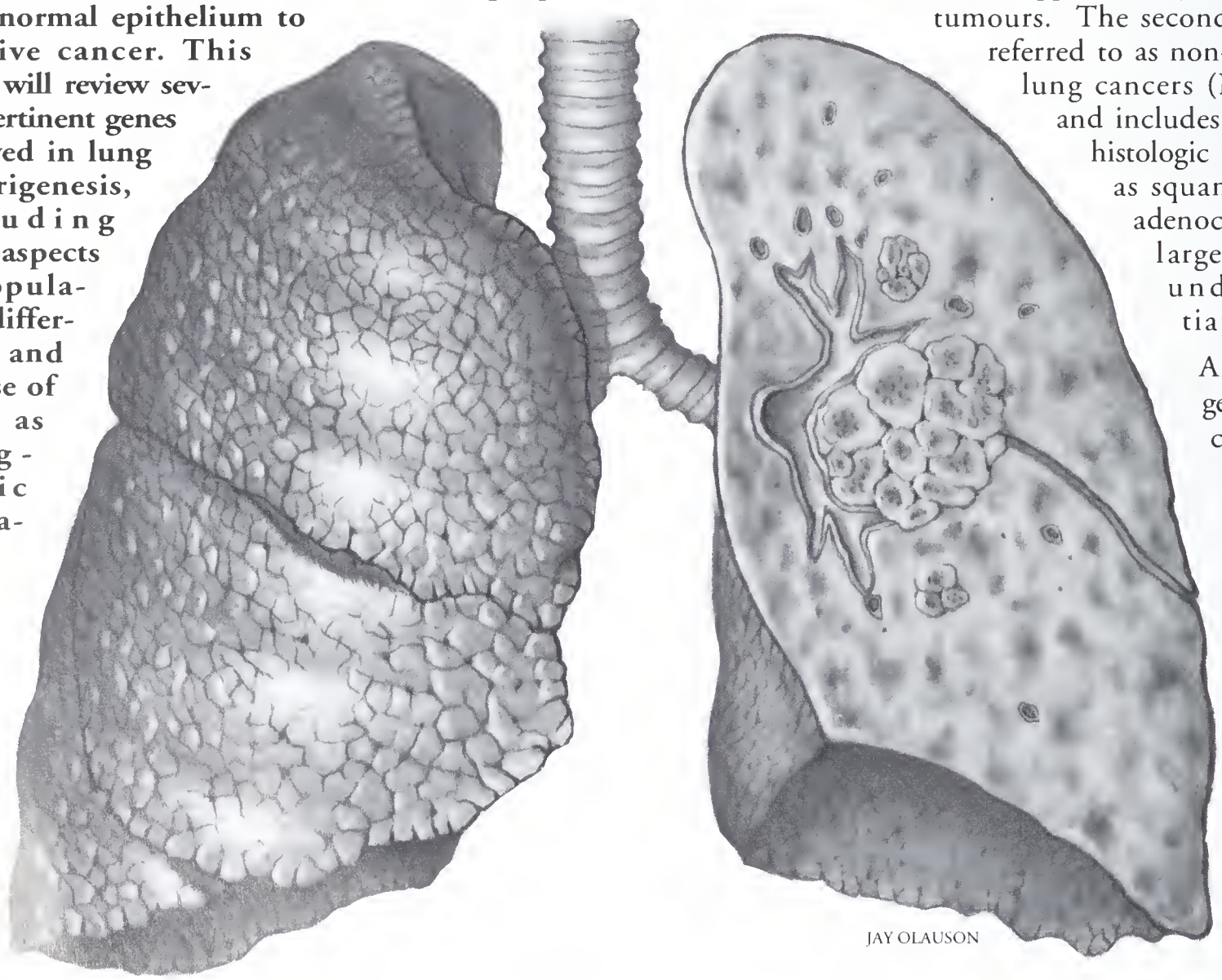
Abstract

The evidence for a genetic basis of human cancer continues to accumulate from various different fields, including epidemiology and molecular genetics. One approach in the search for a genetic basis of lung cancer has focussed on the genetic alterations in certain categories of genes: proto-oncogenes such as *ras* and *myc,* and tumour suppressor genes such as *p53.* Interest has also centred on enzymes such as cytochrome P-450 and the glutathione S-transferases, which are involved in the metabolism of procarcinogens. The genetic alterations are likely only part of the process, as the development of lung cancer is thought to involve a sequence of genetic events which take several years to progress from normal epithelium to invasive cancer. This paper will review several pertinent genes involved in lung tumorigenesis, including some aspects of population differences and the use of genes as prognostic indicators.

Introduction

While the strong influence of tobacco exposure on lung cancer development obscures genetic influences, there are indications that aspects of cancer susceptibility may have a heritable basis. Inherent predisposition to lung cancer has long been suspected, and recent investigations suggest several potential mechanisms[1]. Lung cancers are thought to arise from the sequential accumulation of multiple genetic mutations, the number estimated to be in double digits[2]. The morphological changes take several years to progress from normal epithelium to hyperplasia, metaplasia, dysplasia, carcinoma in situ, invasive cancer and finally metastatic cancer. Lung cancers are generally divided into two groups. The first is the small cell lung cancers (SCLCs), which account for approximately 25% of lung tumours. The second group is referred to as non-small cell lung cancers (NSCLCs) and includes the other histologic types such as squamous cell, adenocarcinoma, large cell, and undifferentiated.

Among the genes which control cell proliferation and



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differentiation that have been implicated in carcinogenesis are proto-oncogenes and tumour suppressor genes. Dominant proto-oncogenes become "activated" to oncogenes through particular mutations, resulting in overexpression of the normal protein or production of a mutant protein. Conversely, tumour suppressor gene products normally block abnormal growth and malignant transformation. A single functional copy of a tumour suppressor gene sustains a normal phenotype. When one copy is lost, by either germline or somatic mutation, acquiring a somatic mutation at the remaining allele results in a cell lacking the ability to suppress tumour development[3]. Thus, in contrast to proto-oncogenes, mutations in tumour suppressor genes are recessive in their action. Other genes which are thought to play a role in carcinogenesis include the cytochrome P-450 and glutathione S-transferase genes. The products of these genes are enzymes which participate in the metabolism of procarcinogens. Genetic differences in the expression of these genes may be at least partly responsible for differences in susceptibility to lung cancer.

With respect to epidemiology, lung cancer is the most common cause of cancer death among Canadian men and women. In 1994, it was estimated that 11,000 men and 5,600 women died of lung cancer. It ranks second in terms of number of new cases of cancer (after prostate cancer for men and breast cancer for women), with an estimated 12,700 cases among men and 6,900 among women in 1994[4]. While mortality and incidence rates of lung cancer have been relatively stable among men over the last decade, these figures are still increasing among women[4].

The case-fatality ratio (deaths/incidence ratio) is relatively high compared to other common cancers, and is estimated at 87% and 81% for men and women respectively in 1994[4]. Moreover, the 5-year relative survival rates have not improved between the 1970's and the 1980's; for those diagnosed in 1970-74, the relative 5-year survival rates for men and women were 13% and 18%[5]. For cases diagnosed in 1980-84, these figures were 12% and 16%.

The intent of this review is to discuss several pertinent oncogenes, tumour suppressor genes, and metabolic enzymes involved in the development of neoplasms of the lung. Both the small and non-small cell types will be considered, as well as prognostic significance of the genes, and distribution differences among various populations of the world.

The *p53* gene

The *p53* gene encodes a nuclear protein that has several functions, among which is the role of transcription factor[2]. The normal *p53* gene product negatively regulates cell growth and division, whereas mutated forms can stimulate cell division. In addition, replacement of wild-type *p53* in lung cancer cells inhibits growth and tumorigenicity, suggesting that *p53* acts as a master growth regulatory switch[3]. The *p53* mutations may therefore offer a growth advantage, and thus allow the growth of cancer cells.

The wild-type of *p53* protein exists in at least two forms among human populations, due to amino acid replacement of Arg by Pro at codon 72[6]. An increased frequency of the Pro allele in a population may be linked to an elevated risk of developing lung cancer. For example, the germline Arg to Pro polymorphism is associated with an increased susceptibility in a Japanese population: a Pro/Pro genotype has a 1.7-fold higher risk of smoking-induced lung cancer compared with other genotypes[6]. The allele frequency of the *p53* Arg allele among American caucasians was similar to that among the Japanese (0.71), but was less common in African-Americans (0.50)[7]. However, no association with a diagnosis of lung cancer was observed in this latter population[8]. Weston *et al*[7] found the Pro variant at codon 72 more prevalent in adenocarcinoma patients in comparison with other histologies, implying a propensity for one histological type. Perhaps future studies may reveal a link between the Pro variant and only certain lung cancer types.

Mutations of the *p53* tumour suppressor gene are proving to be the most common genetic alteration in human cancer[7,9], occurring in more than one half of all lung cancers[2]. The types of point mutations in the *p53* gene vary considerably in different kinds of human cancers. In lung cancer, *p53* mutations are most commonly G to T transversions (change from a purine to a pyrimidine), whereas G to A transitions predominate in other cancers[2], suggesting that specific carcinogens are involved[9,10,11]. Since one of the components of tobacco smoke is benzo(a)pyrene, a potent mutagen that causes G:C to T:A transversions, a correlation between smoking and these particular mutations might be expected[12]. Indeed, *p53* mutations show a significant association with a history of smoking[10]. Conversely, in a study of radon miners, it was found that the mutations did not occur at the "hotspot" codons described in lung cancer, and were not of the usual G:C to T:A transversions associated with tobacco smoking[13]. These differences may be attributable to the specific genotoxic effects of radon.

The *p53* mutations are found in early and late clinical stages, providing evidence that the *p53* mutations occur most often as a relatively early event[3,14]. In fact, *p53* alterations have even been detected in preneoplastic lesions of the lung[15]. The possibility arises that screening for *p53* mutations could form the basis for early detection of lung cancer. Mao *et al*[16] reported the

detection of oncogene mutations in sputum, preceding the clinical diagnosis of lung cancer by up to 13 months. In their study, the primary lung carcinomas from 10 of these 15 patients contained either a *ras* or a *p53* gene mutation. In 8 of 10 patients, the identical mutation found in the primary tumour was also detected in at least one sputum sample. This technique, if proven to be effective, could have an enormous impact on lung cancer screening in the future.

Studies have also looked at the possibility of correlating *p53* mutations with clinicopathologic findings or clinical outcome of NSCLC. For example, *p53* mutation is correlated with significantly shorter survival after surgery, and is also a prognostic factor in those with advanced disease[17,18]. Mitsudomi *et al* [18] found no correlation with clinical stage except in squamous cell tumours. Marchetti *et al* [19] found *p53* alterations to be significantly linked with metastatic involvement of hilar and mediastinal lymph nodes. Since the latter are well established prognostic factors for NSCLC, *p53* aberrations may also be a predictor of tumour aggressiveness. Controversy persists, however, as others discovered no apparent association[2,20].

The *myc* genes

The *myc* family of cellular oncogenes encodes at least three highly related nuclear phospho-proteins (c-*myc*, N-*myc*, and L-*myc*). *myc* family genes are differentially expressed with respect to tissue type. Their unique patterns of expression in developing embryos support the view that myc-encoded proteins are involved in gene expression during growth and differentiation[21]. The precise function of myc proteins has not been established, but they may be transcription factors[12]. The application of new biotechnological tools such as transfection vectors may lead to a better understanding of the importance of the myc family of oncogenes.

Activation of *myc* is thought to occur by gene amplification or overexpression of the protein, but not by point mutations[22]. However, the role of *myc*-oncogene amplification or overexpression in tumourigenesis is still not clear. Nevertheless, DNA amplification of cellular proto-oncogenes is a well-established and common mechanism of oncogene activation in several types of human tumours, including the rapidly fatal SCLC. Approximately one fourth of primary SCLC tumours contain amplified copies of one of the three *myc* proto-oncogenes[23]. More specifically, overexpression of *c-myc* has been shown among tumours in contrast to normal tissue, and was significantly more prevalent in large-cell cancers than in adenocarcinoma[24]. In general, the presence of the *myc* genes in SCLC identifies poor patient response to therapy and poor survival[25].

The L-*myc* gene sequence has a restriction site (*Eco*RI) polymorphism between the second and third exons. Inheritance of the alleles containing the restriction site was reported to confer poor prognosis (presence of lymph node metastases) in Japanese lung cancer patients[8]. This hypothesis was tested in both case-control study subjects and additional surgical cases, but no evidence was found to support the hypothesis in the U.S. population. The polymorphism was more frequent in African-Americans (0.71) than caucasians (0.49)[7], but there does not appear to be any relationship between clinical stage of lung cancer and L-*myc* alleles in either group[8]. The reasons for this apparent contradiction are unclear, but a genetic difference related to ethnicity could exist between populations, even though the allelic frequencies do not differ significantly. For example, if one ethnic group consistently seeks medical attention at a later stage, or the cases are associated with a particular histology, bias could result.

The *ras* genes

The *ras* genes (K-*ras*, H-*ras*, and N-*ras*) encode highly homologous proteins which play a role in transmembrane signalling, thereby regulating cellular proliferation. They normally bind guanine nucleotides such as guanosine triphosphate (GTP), and are thought to be in an active state for signalling when GTP is bound, and inactive when the GTP has been hydrolysed to GDP. Point mutations in codons 12, 13 or 61 are believed to prevent GTP hydrolysis, presumably by trapping the protein in the active form[22]. Thus, mutations of the *ras* proteins contribute to the development of cancer, and occur in approximately 20% of NSCLC tumours and tumour cell lines[2]. In NSCLC, mutations of K-*ras* comprise 90% of cases, and are reported in approximately one third of lung adenocarcinomas[26]. In contrast, these mutations have not been found in SCLC tumours or tumour cell lines.

Two studies have stated that K-*ras* mutations are an early and irreversible event in the development of adenocarcinoma of the lung[14,27]. Codon 12 mutations of the K-*ras* gene have been detected in approximately 20% of adenocarcinomas, and in coexisting moderate to severe atypical bronchioloalveolar cell hyperplasia[28], thus reinforcing the belief that this mutation is an early event. Studies also suggest that smoking is an important factor in the induction of these mutations, as point mutations in codon 12 of the K-*ras* proto-oncogene occur more frequently in lung adenocarcinomas from smokers (30%) than from nonsmokers (7%)[27].

Research has also attempted to examine the possibility of coincident alterations. Bongiorno *et al* [29] found that the presence of K-*ras* mutation did not correlate with *p53* accumulation in adenocarcinomas, and thus, concluded that the two mutations define two separate groups of patients. Likewise, in a Japanese study,

coincident abnormalities of K-*ras* and *p53* were not found[30]. Although these genes may be involved to some extent in the pathogenesis of lung cancer, more factors are required for its development.

Interestingly, a study by Lung e*t al*[31] prompted by the unusually high incidence of lung adenocarcinomas among women in Hong Kong revealed K-*ras* point mutations in only 6 adenocarcinomas and one squamous cell carcinoma, all in men, out of a total of 130 lung carcinomas. Although several studies have demonstrated a role for *ras* mutations in adenocarcinoma of the lung, it appears that in Hong Kong, differences in either genetic or environmental influences must also be considered.

Patients whose lung tumour contains a K-*ras* oncogene mutation have been shown to have a worse prognosis[29]. In general, its presence in NSCLC identifies poor patient response to therapy and poor survival[25]. In particular, two retrospective studies have associated K-*ras* mutations in NSCLC tumours with shortened survival. Slebos *et al*[32] found that patients with early-stage adenocarcinoma of the lung lived a shorter period of time following surgical resection. Mitsudomi *et al*[33] confirmed these findings in a group of NSCLCs which included patients with both early- and advanced-stage disease. The patients who had tumours with mutations in the 12th codon of the K-*ras* oncogene survived for a shorter time following tissue sample acquisition than those who did not[33]. While the use of *ras* as a clinical marker is still in the research stages, it is hoped that in the future, it will become a diagnostic and prognostic tool useful in staging and defining treatment plans[25].

Glutathione S-Transferases

The cytosolic glutathione S-transferases (GSTs) are comprised of four multigene families (alpha, mu, pi, and theta). Within the mu class, the *GSTM1* gene is polymorphic, containing two well-characterized genes and a third null allele. Several studies have shown that *GSTM1* is only expressed in 50-55% of Caucasians[34,35]. GSTs are capable of detoxifying a number of carcinogenic electrophiles, including the metabolites of aromatic hydrocarbon procarcinogens activated by CYP1A1 (a cytochrome P-450 polymorphism). Of the numerous components of tobacco smoke, the polycyclic aromatic hydrocarbons (PAHs) appear to be the principal compounds that yield substrates for these enzymes. Accordingly, the absence of *GSTM1* has been implicated in tobacco-related carcinogenesis, as patient variation in GST function may be related to differences in risk for smoking-related cancer[35]. In addition to its presence or absence, the number of copies of the GST-*mu* gene appears to determine activity of the GST-mu enzyme in the lung[35].

Two epidemiological studies have been carried out in which a possible correlation between the absence of *GSTM1* and lung cancer incidence is considered. In the first, involving a U.S. population sample, smokers with and without lung cancer were phenotyped, and a highly significant correlation between the absence of *GSTM1* activity and adenocarcinoma of the lung was observed[36]. In the second, involving genotyping of a British population, the correlation between the homozygous GSTM1 null genotype and lung cancer was much less significant and concerned squamous-cell carcinoma[37]. However, the correlation with squamous cell carcinoma was duplicated in a similar study by Nazar-Stewart *et al*[35], who determined an odds ratio (OR) of 2.1. The role of tobacco smoke has also been considered. Studies by Hirvonen *et al*[34] and Kihara *et al*[38] support the association between the null genotype and smoking-related lung cancer, a risk which appears to be dependent on the extent of tobacco smoke exposure.

Cytochrome P-450

The cytochrome P-450 participate in the metabolic activation of procarcinogens. Genetic differences in this metabolic activity may in part determine individual predisposition to cancer. Recent results reveal that many P-450 genes are polymorphically distributed, including *CYP1A1, CYP2D6* and *CYP2E1*[39]. Different investigators have tried to link these three variants to the incidence of lung cancer. It appears that interesting interethnic differences in the *CYP1A1* gene could be of importance in understanding differences in susceptibility to lung cancer. The data regarding *CYP2D6* and *CYP2E1* are less promising.

CYP1A1 metabolically activates procarcinogens in cigarette smoke such as PAHs, and benzo(a)pyrene, which is also an inducer of *CYP1A1*. Three polymorphisms of the *CYP1A1* gene have been identified with the restriction enzyme MspI: the predominant homozygous allele (A type), the heterozygote (B type), and the homozygous rare allele (C type)[40]. In addition, this MspI restriction site polymorphism has been found to be closely linked to another Ile-Val polymorphism[41].

These two polymorphisms of the *CYP1A1* gene have been associated with lung cancer risk in a Japanese population[40,42], the contribution of the *CYP1A1* gene being independent of the *p53* polymorphism[6]. This association has been studied in terms of genotype frequencies and cigarette smoking dose. Patients with genotype C contracted squamous cell carcinoma after fewer cigarettes than those with other genotypes, with a markedly high risk (OR=7.31) at a low dose level of cigarette smoking. The difference in susceptibility between genotypes was reduced at high dose levels of

cigarette smoking[43]. A further increased risk (OR=16) was observed for individuals with the susceptible *Msp*I or Ile-Val genotype combined with a deficient genotype of *GSTM1,* also at a low dose level of cigarette smoking[44]. However, it appears that there may be significant differences in risk between ethnic origins. Firstly, the Ile-Val allele is about three times more frequent in Japan than in caucasians from Norway and the USA, in which no correlation has been found between this allele and lung cancer[42,45]. In contrast, Drakoulis *et al* [41] did find the Ile-Val polymorphism to be more prevalent in lung cancer patients than in controls within a German study group. With respect to the MspI allele, Shields *et al* [46] reported an increased frequency of the allele in African compared to caucasian Americans (OR=2.9), but found no association with lung cancer risk. Studies of other caucasian populations, including German[41], Brazilian[47], Finnish[48], Swedish, and Norwegian[45] populations also revealed no apparent increased risk.

A second cytochrome P-450 enzyme polymorphism, *CYP2D6,* controls the ability to metabolize compounds such as debrisoquine (a ß-adrenergic blocking agent), and has also been associated with an increased susceptibility to lung cancer, although controversially. Individuals homozygous for the defective allele are classified as "poor metabolizers", whereas those either homozygous or heterozygous for the *CYP2D6* wild type alleles were classified as "extensive metabolizers" of debrisoquine. Poor metabolizers are thought to be less prone to develop cancer, theoretically because less activation of procarcinogens occurs. This relation is demonstrated by the fact that poor metabolizers tend to be underrepresented among patients with lung cancer[48,49]. However, Hirvonen *et al* [26] observed no significant difference in the allelic frequencies between lung cancer patients with a history of heavy smoking and those who smoked less. Based on the hypothesis of procarcinogen activation, one might expect the poor metabolizers to be underrepresented among the heavy smoking group, if it were a dose-related relationship[48].

The *CYP2E1* gene has also been evaluated for a possible association with lung cancer, but with less success. Similar to the findings of the *CYP1A1* gene, a Japanese study reported a significant difference in the distribution of the genotypes for the *Dra*I polymorphism among lung cancer patients compared with controls,[50] but again, studies of Swedish and Finnish populations failed to verify these findings[48,51]. It would appear that interethnic differences exist, which may be related to the frequencies of these alleles in the different populations. Persson *et al* [51] report frequencies in the range of 0.08 - 0.18 among the Swedish population, in contrast to approximately 0.26 among the Japanese[51]. This difference may represent part of the reason for the apparent risk discrepancy among races.

It appears that there has been some success in linking the *CYP1A1, CYP2D6* and *CYP2E1* genes to the incidence of lung cancer. However, the interethnic differences hinder the ability to extrapolate results between different ethnic groups. Clearly, more research is required in order to properly define the role of the cytochrome P-450 genes in lung tumourigenesis.

Conclusion

With the epidemiological evidence presented, it is evident lung cancer continues to burden humanity. In Canada, lung cancer remains the most common cause of cancer death. Unfortunately, the incidence and mortality of lung cancer is increasing among women, and the prognosis for lung cancer is extremely poor.

Many studies have been undertaken to determine the mutational events that are key to particular cancers. Through advances in molecular genetics, it has become apparent that there exist a number of genes which control cell proliferation and differentiation. Numerous molecular genetic changes are present in lung cancer, some of which (e.g. mutated oncogenes) are found in other tumours. These mutations provide clues about the carcinogenesis and pathogenesis of lung cancer. As the details of the carcinogenic process are unravelled, one goal is to identify intermediate (preneoplastic) markers of exposure and inherent predisposition that will help assess the risk of lung cancer for individuals as well as for groups. With this knowledge, new directions in prevention and treatment will allow an improved prognosis for the future.

References

1. Davila DG, Williams DE. The etiology of lung cancer. Mayo Clinic Proceedings 1993; 68(2): 170-82.
2. Johnson BE, Kelley MJ. Overview of genetic and molecular events in the pathogenesis of lung cancer. Chest 1993; 103 (1 Suppl): 1S-3S.
3. Minna JD. The molecular biology of lung cancer pathogenesis. Chest 1993; 103 (4 Suppl): 449S-456S.
4. National Cancer Institute of Canada: Canadian Cancer Statistics 1994 Toronto, Canada, 1994.
5. National Cancer Institute of Canada: Canadian Cancer Statistics 1993 Toronto, Canada, 1993.
6. Kawajiri K, Nakachi K, Imai K, Watanabe J, Hayashi S. Germ line polymorphisms of p53 and CYP1A1 genes involved in human lung cancer. Carcinogenesis 1993; 14(6): 1085-9.
7. Weston A, Caporaso NE, Perrin LS, et al. Determination of the allele frequencies of an L-myc and a p53 polymorphism in human lung cancer. Carcinogenesis 1994; 15(4): 583-7.
8. Weston A, Caporaso NE, Perrin LS, et al. Relationship of H-ras-1, L-myc, and p53 polymorphisms with lung cancer risk and prognosis. Environmental Health Perspectectives 1992; 98: 61-67.
9. Kandioler D, Foedinger M, Mueller MR, Eckersberger F, Mannhalter C, Wolner E. Carcinogen-specific mutations in the p53 tumor suppressor gene in lung cancer. Journal of Thoracic & Cardiovascular Surgery 1994; 107(4): 1095-8.

10. Ryberg D, Kure E, Lystad S, et al. p53 mutations in lung tumors: relationship to putative susceptibility markers for cancer. Cancer Research 1994; 54(6): 1550-5.
11. Reichel MB, Ohgaki H, Petersen I, Kleihues P. p53 mutations in primary lung tumors and their metastases. Molecular Carcinogenesis 1994; 9(2): 105-9.
12. Anderson ML, Spandidos DA. Oncogenes and onco-suppressor genes in lung cancer. Respiratory Medicine 1993; 87(6): 413-20
13. Vahakangas KH, Samet JM, Metcalf RA, et al. Mutations of p53 and ras genes in radon-associated lung cancer from uranium miners. The Lancet 1992; 339(8793): 576-80.
14. Li ZH, Zheng J, Weiss LM, Shibata D. c-k-ras and p53 mutations occur very early in adenocarcinoma of the lung. Amercian Journal of Pathology 1994; 144(2): 303-9.
15. Sozzi G, Miozzi M, Donghi R, et al. Deletions of 17p and p53 mutations in preneoplastic lesions of the lung. Cancer Research 1992; 52(21): 6079-82.
16. Mao L, Hruban RH, Boyle JO, Tockman M, Sidransky D. Detection of oncogene mutations in sputum precedes diagnosis of lung cancer. Cancer Research 1994; 54(7): 1634-7.
17. Horio Y, Takahashi T, Kuroishi T et al. Prognostic significance of p53 mutations and 3p deletions in primary resected non-small cell lung cancer. Cancer Research 1993; 53(1): 1-4.
18. Mitsudomi T, Oyama T, Kusano T, Osaki T, Nakanishi R, Shirakusa T. Mutations of the p53 gene as a predictor of poor prognosis in patients with non-small-cell lung cancer. Journal of the National Cancer Institute 1993; 85(24): 2018-23.
19. Marchetti A, Buttitta F, Merlo G, et al. p53 alterations in non-small cell lung cancers correlate with metastatic involvement of hilar and mediastinal lymph nodes. Cancer Research 1993; 53(12): 2846-51.
20. Casson AG, McCuaig S, Craig I, et al. Prognostic value and clinicopathologic correlation of p53 gene mutations and nuclear DNA content in human lung cancer: a prospective study. Journal of Surgical Oncology 1994; 56(1): 13-20.
21. Prins J, De Vries EG, Mulder NH. The myc family of oncogenes and their presence and importance in SCLC and other tumour types. Anticancer Research 1993; 13(5A): 1373-85.
22. Anderson ML, Spandidos DA. Oncogenes and onco-suppressor genes in lung cancer. Respiratory Medicine 1993; 87(6): 413-20.
23. Makela TP, Saksela K, Alitalo K. Amplification and rearrangement of L-myc in human small-cell lung cancer. Mutation Research 1992; 276(3): 307-15.
24. Lorenz J, Friedberg T, Paulus R, Oesch F, Ferlinz R. Oncogene overexpression in NSCLC tissue: prevalence and clinicopathological significance. Clinical Investigator 1994; 72(2): 156-63.
25. Kern JA, Filderman AE. Oncogenes and growth factors in human lung cancer. Clinics in Chest Medicine 1993; 14(1): 31-41.
26. Hirvonen A, Husgafvel-Pursiainen K, Anttila S, Karjalainen A, Pelkonen, Vainio H. PCR-based CYP2D6 genotyping for Finnish lung cancer patients. Pharmacogenetics 1993; 3(1): 19-27.
27. Westra WH, Slebos RJ, Offerhaus GJ, et al. K-ras oncogene activation in lung adenocarcinomas from former smokers. Evidence that K-ras mutations are an early and irreversible event in the development of adenocarcinoma of the lung. Cancer 1993; 72(2): 432-8.
28. Ohshima S, Shimizu Y, Takahama M. Detection of c-Ki-ras gene mutation in paraffin sections of adenocarcinoma and atypical bronchioloalveolar cell hyperplasia of human lung. Virchows Archives 1994; 424(2): 129-34.
29. Bongiorno PF, Whyte RI, Lesser EJ, Moore JH, Orringer MB, Beer DG. Alterations of K-ras, p53, and erbB-2/neu in human lung adenocarcinomas. Journal of Thoracic & Cardiovascular Surgery 1994; 107(2): 590-5.
30. Kashii T, Mizushima Y, Monno S, Nakagawa K, Kobayashi M. Gene analysis of K-, H-ras, p53, and retinoblastoma susceptibility genes in human lung cancer cell lines by the polymerase chain reaction/single-strand conformation polymorphism method. Journal of Cancer Research & Clinical Oncology 1994; 120(3): 143-8.
31. Lung ML, Wong M, Lam WK, et al. Incidence of ras oncogene activation in lung carcinomas in Hong Kong. Cancer 1992; 70(4): 760-3.
32. Slebos RJC, Kibbelaar RE, Dalesio O, et al. K-ras oncogene activation as a prognostic marker in adenocarcinoma of the lung. New England Journal of Medicine 1990; 323(9): 561-5.
33. Mitsudomi T, Steinberg SM, Oie HK, et al. ras gene mutations in non-small-cell lung cancers are associated with shortened survival irrespective of treatment intent. Cancer Research 1991; 51(18): 4999-5002.
34. Hirvonen A, Husgafvel-Pursiainen K, Anttila S, Vainio H. The GSTM1 null genotype as a potential risk modifier for squamous cell carcinoma of the lung. Carcinogenesis 1993; 14(7): 1479-81.
35. Nazar-Stewart V, Motulsky AG, Eaton DL, et al. The glutathione S-transferase mu polymorphism as a marker for susceptibility to lung carcinoma. Cancer Research 1993; 53 (10 Suppl): 2313-8.
36. Seidegard J, Pero RW, Markowitz MM, Roush G, Miller DG, Beattie EJ. Isoenzymes of glutathione transferase (class mu) as a marker for the susceptibility to lung cancer: a follow up study. Carcinogenesis 1990; 11(1): 33-36.
37. Zhong S, Howie AF, Ketterer B, et al. Glutathione S-transferase mu locus: use of genotyping and phenotyping assays to assess association with lung cancer susceptibility. Carcinogenesis 1991; 12(9): 1533-7.
38. Kihara M, Kihara M, Noda K. Lung cancer risk of GSTM1 null genotype is dependent on the extent of tobacco smoke exposure. Carcinogenesis 1994; 15(2): 415-8.

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39. Ingelman-Sundberg M, Johansson I, Persson I, et al. Genetic polymorphism of cytochromes P450: interethnic differences and relationship to incidence of lung cancer. Pharmacogenetics 1992; 2(6): 264-71.
40. Kawajiri K, Nakachi K, Imai K, Hayashi S, Watanabe J. Individual differences in lung cancer susceptibility in relation to polymorphisms of P-4501A1 gene and cigarette dose. International Symposium of the Princess Takamatsu Cancer Research Fund 1990; 21: 55-61.
41. Drakoulis N, Cascorbi I, Brockmoller J, Gross CR, Roots I. Polymorphisms in the human CYP1A1 gene as susceptibility factors for lung cancer: exon-7 mutation (4889 A to G), and a T to C mutation in the 3'-flanking region. Clinical Investigator 1994; 72(3): 240-8.
42. Kawajiri K, Nakachi K, Imai K, Yoshii A, Shinoda N, Watanabe J. Identification of genetically high risk individuals to lung cancer by DNA polymorphisms of the cytochrome P450IA1 gene. FEBS Letters 1990; 263(1); 131-3.
43. Nakachi K, Imai K, Hayashi S, Watanabe J, Kawajiri K. Genetic susceptibility to squamous cell carcinoma of the lung in relation to cigarette smoking dose. Cancer Research 1991; 51(19): 5177-80.
44. Nakachi K, Imai K, Hayashi S, Kawajiri K. Polymorphisms of the CYP1A1 and gluatathione S-transferase genes associated with susceptibility to lung cancer in relation to cigarette dose in a Japanese population. Cancer Research 1993; 53(13): 2994-9.
45. Tefre T, Ryberg D, Haugen A, et al. Human CYP1A1 (cytochrome P(1)450) gene: lack of associaton between the MspI restriction fragment length polymorphism and incidence of lung cancer in a Norwegian population. Pharmacogenetics 1991; 1(1): 20-25.
46. Shields PG, Caporaso NE, Falk RT, et al. Lung cancer, race, and a CYP1A1 genetic polymorphism. Cancer Epidemiology, Biomarkers Biomarkers & Prevention 1993; 2(5): 481-5.
47. Sugimura H, Suzuki I, Hamada GS, et al. Cytochrome P-450 1A1 genotype in lung cancer patients and controls in Rio de Janeiro, Brazil. Cancer Epidemiology, Biomarkers & Prevention 1994; 3(2): 145-8.
48. Hirvonen A, Husgafvel-Pursiainen K, Anttila S, Karjalainen A, Sorsa M, Vainio H. Metabolic cytochrome P450 genotypes and assessment of individual susceptibility to lung cancer. Pharmacogenetics 1992; 2(6): 259-63.
49. Agundez JA, Martinez C, Ladero JM, et al. Debrisoquine oxidation genotype and susceptibility to lung cancer. Clinical Pharmacology & Therapeutics 1994; 55(1): 10-14.
50. Uematsu F, Kikuchi H, Motomiya M, et al. Human cytochrome P450IIE1 gene: DraI polymorphism and susceptibility to cancer. Tohoku Journal of Experimental Medicine 1992; 168(2): 113-7.
51. Persson I, Johansson I, Bergling H, et al. Genetic polymorphism of cytochrome p4502E1 in Swedish population. FEBS Lett 1993; 319(3): 207-11.

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Cystic Fibrosis: A Clinical, Molecular and Therapeutic Perspective

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Abstract

Cystic fibrosis (CF) is an autosomal recessive disease with an incidence of approximately 1/2500 live births. The major clinical pathology common to CF is the accumulation of mucus in the lower airways leading to chronic opportunistic respiratory infection and airway blockage. Although the average life span of individuals with cystic fibrosis has been steadily increasing due mostly to advances in pathogen control and mucus clearance, their life expectancy remains severely compromised. The cloning of the gene responsible for cystic fibrosis (CFTR) in 1989 heralded the dawn of a massive effort aimed at understanding and treating the basic defect underlying this disease at the molecular level. Although more has been learned about the pathophysiology of CF in the last five years than in all the preceeding years, much has yet to be learned, and the paramount goal of a lasting cure for CF has yet too be achieved.

In this review we will deal with the clinical consequences of CF, the understanding of the disease at both the molecular level and through the utilization of animal models, and finally, the current and proposed therapeutic interventions derived from these studies to ameliorate the course of the disease.

Cystic Fibrosis: A Clinical Perspective

The most common clinical presentations of cystic fibrosis (CF) are chronic respiratory disorders, high levels of sweat electrolytes and abnormal gastrointestinal function.

Although CF presents a multitude of clinical symptoms, the major site of morbidity as well as the cause of mortality in approximately 95% of CF patients results from severe lung dysfunction. The primary pathological abnormalities of the lungs are the hypertrophy of the mucus glands and mucus hypersecretion[1]. The pulmonary manifestations of CF generally begin as a mild cough early in life. Over time, the frequency and severity of the persistent coughing increases leading to a corresponding increase in pulmonary damage, respiratory failure and

eventually death of the afflicted individual. A typical characteristic of the pulmonary disease in CF patients is the presence of respiratory infections. The mucus layer of the airways demonstrates overall reduced clearance kinetics due to its increased viscosity[2]; it is thought that the stagnant mucus provides a fertile media for the growth of opportunistic pathogens. Although the pathogens present in CF lungs may be quite diverse, the three most commonly identified types of bacteria are P. *aeruginosa,* S. *aureus* and H. *influenza* [3]. The chronic presence of these pathogens is thought to be the initial causative factor leading to a cascade of secondary consequences including stimulation of additional mucus secretions, tissue damage and airway inflammation which results in increasing damage to the lungs. With more accurate clinical tests for CF enabling earlier diagnosis of the disorder, the progression of the lung disease has been slowed by the administration of antibiotics earlier in life. Additional abnormalities in the respiratory tract of CF individuals include an increased occurrence of nasal polyps, usually beginning in early childhood. It has been determined that 6-24% of patients will develop nasal polyps which are generally removed surgically[4].

In addition, the defective chloride reabsorptive function of CF sweat glands results in the presence of high concentrations of chloride as well as sodium in the sweat of CF patients[5]. As a consequence of the high electrolyte levels present in their sweat, excessive sweating may result in heat prostration giving rise to metabolic alkalosis and the dehydration of CF individuals[6].

The primary cause of much of the gastrointestinal abnormalitites associated with cystic fibrosis results from inadequate exocrine pancreatic secretions[7]. Aproximately 85% of CF patients show a marked decrease in pancreatic enzyme release which shows a drastically diminished response to hormonal stimulation leading to a "failure to thrive syndrome". The residual exocrine pancreatic secretions of typical CF patients are dehydrated and show decreased levels of sodium bicarbonate[8]. The accumulation of the inspissated secretions are thought to obstruct the small pancreatic ducts which gives rise to the dilation of the pancreatic acini[9]. Furthermore, the decreased presence of sodium bicarbonate in the duodenal secretions results in a higher incidence of gastroduodenal ulcers in CF patients[10]. In addition to the diminished exocrine pancreatic insufficiency, an inadequate endocrine pancreatic function may be responsible for a higher then expected frequency of diabetes mellitus in CF patients[11]. This manifestation may be due to the atrophy of the pancreas including the islets of Langerhans with age. The degeneration of the islets of Langerhans may lead to endocrine pancreatic inadequacy resulting in diminished insulin production for normal cellular glucose uptake.

Roughly 10% of CF newborns display an obstruction of the intestinal tract at or soon after birth[12]. This manifestation is termed meconium ileus and results from the presence of a dehydrated meconium mass in the intestinal tract. A later onset intestinal obstruction (distal intestinal obstruction syndrome or meconium ileus equivalent) in CF patients is also commonly observed and may involve the ileum, appendix, cecum and ascending colon[13]. The obstructive disorder in the latter manifestation results from the accumulation of dehydrated chyme which results in lesions and potential perforations of the adjacent mucosal epithelia and may lead to peritonitis[14]. Although the etiology of meconium ileus equivalent is not entirely known, the involvement of inadequate hydration of secreted mucins has been implicated. In addition, another common intestinal consequence of cystic fibrosis is rectal prolapse which results from the passing of soft stools and inadequate abdominal muscle strength[15].

Involvement of the liver is also commonly observed in cystic fibrosis. The major pathological changes of the liver are the distension of the small bile ducts, bile duct proliferation, and the infiltration of fatty tissue resulting in hepatic enlargement[16]. Furthermore, approximately 30% of CF patients develop cystic duct atresia and a small gallbladder[17].

It has also been noted that CF males are not fertile. This male sterility has been attributed to the congenital atrophy of the vas deferens and epididymis[18], possibly due their obstruction during development.

Cystic Fibrosis: A Molecular Perspective

The gene responsible for CF (CFTR) spans 250 kilobases of DNA at position q31 of chromosome 7. The CFTR gene contains 27 exons and produces a transcript of approximately 6.5 kilobases[19]. The resulting protein product of CFTR was determined to be 180 kDa and related to a family of membrane transport proteins each containing 12 membrane spanning segments and two ATP binding domains[20]. The distribution of CFTR expression in both rodent and human tissues[21,22] and its ability to correct the cAMP-regulated chloride channel defect in CF cells[23] confirmed that CFTR is the gene accountable for CF.

The basic defect

Although pathological abnormalities of CF indicated that the basic defect associated with CF was in chloride transport across apical membranes of epithelial cells; its conclusive proof awaited the expression and characterization of the CFTR protein *in vitro.* These studies did indeed reveal that the CFTR protein product itself functioned as a cAMP-regulated chloride channel in tissue culture cell lines as well as synthetic lipid bilayers[24,25]. Investigation into the regulation of the CFTR protein determined that cAMP-dependant PKA mediated phosphorylation[26] of CFTR and binding (but not necessarily hydolysis[27]) of ATP by the two ATP-binding domains were necessay for its chloride transport function. Although it has also been reported that the CFTR protein may play a role in acidification of intracellular organelles[28] or may be involved in membrane trafficking[29], the effect of these putative secondary functions on disease pathogenesis is not fully understood. In

addition, concurrent to the diminished chloride transport across apical membranes of epithelial cells from CF tissues, a corresponding abnormality in sodium transport has also been noted[30]. The relationship between the sodium transport abnormalities in CF and CFTR function is not clearly understood.

The confirmation of the basic defect in cystic fibrosis as defective apical membrane electrolyte transport lead to the inferrence of the secondary consequences of the basic defect ensuing from inadequate water transport across luminal epithelia. The diminished water transport is believed to result in a consequential dehydration of luminal secretions (most commonly mucins) causing a blockage of pancreatic ducts, small respiratory airways and the vas deferens, leading to the major clinical symptoms of the disease.

Genotype to phenotype

The research into CFTR mutations resulting in cystic fibrosis has provided a means for the unequivocal diagnosis of CF as well as a basis for the understanding of the structure and function of the CFTR protein.

To date, approximately 50,000 CF chromosomes have been analysed and over 500 DNA sequence variations which may result in cystic fibrosis have been identified by the CF Analysis Consortium. Although the various mutations identified are quite diverse, they can be categorized into several groups according to their resultant level of CFTR protein maturation[31]. The predominant mutation in CFTR which accounts for aproximately 70% of all CF alleles world-wide is a deletion of 3 base pairs in exon 10 resulting in the loss of a phenylalanine residue (Δ508) in the first ATP binding domain[32]. Even though a large number of mutations responsible for cystic fibrosis have thus far been identified, they account for only about 90% of all CF alleles world-wide. It is conceivable that the remaining mutations will most likely be rare and contribute to only a small number of CF alleles.

Clinical investigation of CF patients has determined relative variations between individuals in terms of CF severity. The identification of mutations in CFTR has allowed a correlative study between CFTR genotype and disease phenotype. Although a clear correlation in these studies is not evident, a relationship is observed with respect to genotype and pancreatic function[33]. A class of missense mutations which result in a partially functional CFTR chloride channel lead to clinically milder cases of cystic fibrosis with respect to pancreatic involvement[34], and are thus designated as pancreatic sufficient (PS). These milder mutations may be grouped into two sets according to their location in the gene. The first set (A455E and P574H)[35] are located in the first ATP binding domain and are thought to cause only minor perturbations in the structure leading to a protein with correct post-translational processing but slightly reduced anion transport function. The other class of mild mutations are missense mutations (R117H, R334W and R347P)[36,37] which result in the substitution of basically charged amino acids found in the first transmembrane domain of the protein. The substitutions are into residues with a diminished positive charge at neutral pH and are thought to modify the properties of the channel and thus have a detrimental affect on its conductance of anions[38].

A clear correlation of CF genotype to phenotype is not seen with respect to lung pathology as is evident for the pancreatic involvement[39]; individuals displaying identical CFTR genotypes do not necessarily demonstrate similarly severe lung phenotypes. This lack of relationship between genotype and lung phenotype suggests the involvement of secondary determinants affecting the course of the lung disease. These secondary factors influencing severity may be either genetic, environmental or a combination of both. The identification of these factors and their contribution to the phenotype could provide a greater understanding of the pathophysiology of CF.

Animal models of Cystic Fibrosis

A major step towards to the elucidation and treatment of the basic defect in cystic fibrosis depended on the existence of an animal model manifesting a CF-like pathology. Although no naturally occurring animal model has yet been reported for cystic fibrosis, the generation of mouse models has recently been accomplished using the technique of gene-targeting in mouse embryonic stem cells[40]. This so-called "CF mouse" has been shown to produce no intact CFTR and consequently lack the cAMP-activated chloride channel[41].

CF mice provide an important model for the elucidation of the pathophysiology of cystic fibrosis as well as a potential model for genetic as well as pharmaceutical therapy. The homozygous CF mice exhibited normal birth weights and no obvious prenatal developmental abnormalities. Postnatally the CF mice tended to grow slower than their normal littermates suggesting a failure to thrive during the weaning period. Postmortem examination of the CF mice indicated the most likely cause of death was peritonitis due to intestinal wall rupture. The intestinal tracts in these mice were occluded with a viscous mixture of mucus and fecal matter, reminiscent of meconium ileus in humans. Histological examination of the gastrointestinal tract of the CF mice revealed the dilation of the crypts of Lieberkuhn and their obstruction with a mucus containing inspissation; these complications were coincident with the relatively high levels of CFTR expression found in the intestinal crypt cells. Other abnormalities of the GI tract include morphological changes and reduction of the cecum and the atrophy of Brunner's gland. Severe disease involvement paralleling that of CF in humans in the homozygous mice is also seen in the gallbladder. The gallbladder's of the CF mice are generally distended and in some cases ruptured as a consequence of biliary tract obstruction.

However, unlike CF in humans, the CF mice developed very little pancreatic manifestations of the disease (i.e. pancreatic enzyme insufficiency and pancreatic duct obstruction/atrophy). Although some dilation of the pancreatic acini as well as atrophy of small pancreatic ducts due

to mucus secretions was observed, it was not consistent between the affected mice nor were they as severe as the human cases. Moreover these mice demonstrated no inclination towards pancreatic insufficiency. A similar lack of correlation with CF pathology in humans was noted for the involvement of the liver and especially the reproductive system. In direct contrast to that in humans, the male CF mice which reached reproductive maturity demonstrated normal fertility, while the females showed a notable reduction in reproductive capability.

The system of major importance in terms of mortality in human patients is the respiratory tract; thus an animal model exhibiting a CF-like lung phenotype is crucial to the development of a treatment for cystic fibrosis Although it has been shown that CFTR was expressed in moderate levels in mouse lungs (as is the case for human lungs), the CF mice did not develop any manifestation of small airway obstruction, respiratory tract infection or respiratory mucus hypersecretion. The pulmonary system of these mice remained fully functional and only slight atrophy of serous glands in the nasal sinuses due to their dilation, and possible hyperplasia of goblet cells in the respiratory epithelium was noted. The lack of correlation in lung phenotypes between CF mice and CF patients may have been due to the relatively short lifespan of the CF mice, different lung physiology between the two species, or the presence of a compensatory mechanism (such as a second chloride channel in the pulmonary epithelia) in murine lungs. The observation of a Ca^{++} - activated chloride transport pathway in the respiratory epithelia but lacking in the interstitial epithelia of mice[43] provided support for the latter assumption.

A recent observation from the CF mice has been their decreased susceptibilty to the cholera toxin[42]. Mice which were homozygous for the disruption of the CFTR gene showed a notable decrease in their susceptibility to the bacterium, while heterozygotes showed an intermediate level of disease severity following infection. These results implied that human CF heterozygotes also demonstrate an advantage in terms of resistance to cholera. It has been suggested that this possible "heterozygous advantage" may account for the high prevalence of carriers of CFTR mutations in the population deriving from western Europe, which was historically plagued by numerous outbreaks of cholera.

Cystic Fibrosis: A Therapeutic Perspective

The ultimate goal of research into cystic fibrosis is in its treatment. In this respect, several approaches aimed at both complementing the basic defect or alleviating the secondary consequences of CF have been considered and attempted. Since the lung disease associated with cystic fibrosis is the major cause of morbidity and mortality, the primary emphasis for therapy is focused at this level. Conventional therapy included mechanical removal of the accumulated mucus and aggressive antibiotic treatment to control the growth of pathogens. Although these conventional methods are somewhat effective, they do not provide the absolute treatment for CF.

The treatment of the lung pathology of CF by drug intervention is currently being investigated. These therapies are focused both on the correction of the putative basic defect by the activation of secondary chloride channels[44] as well as the inhibition of the Na^{+} transport[45] in the apical membranes of the lung epithelia. Drug therapies are also focused on the secondary consequences of the lung disease, including decreasing the mucus viscosity[46] and increasing its clearance. Although drug therapy is progressing rapidly, it provides only a short term treatment of CF, long term correction relies on advances in genetic therapy.

The transfer of a functional copy of the CFTR minigene into CF patients is the ultimate goal as well as the paramount challenge for CF research. Since all clinical conditions of CF save the respiratory disease have been successfully conquered with conventional therapeutics, gene replacement therapy is aimed primarily at the lungs. Preliminary studies to demonstrate the feasibility of gene replacement therapy *in vitro* have shown that expression of the cloned CFTR cDNA was able to complement the ion channel defect in CF cells[47]. The success of the early *in vitro* experiments lead *to in vivo* trials of gene transfers into rodents[48,49], human xenografts[50], primates[51] and finally first phase clinical trials of CF patients[52,53].

To begin to treat cystic fibrosis of the lungs, it is important to understand what is defective in CF lungs. The answer to this question is not entirely known, but the expression of CFTR in the lung tissue may provide some indications. Studies in normal human lungs have revealed expression of CFTR early in fetal lung development[22]. Although CFTR is expressed prenatally, there are no obvious pathological changes within the lungs of CF newborns. The observation that CF newborns have relatively healthy lungs implies that postnatal therapeutic intervention may be sufficient to treat the lung pathology. In postnatal human lungs, the expression of CFTR has been observed both in the airway epithelium, where only a small percentage of cells show CFTR expression, and the submucosal glands where it is expressed at relatively high levels[54].

Further considerations for gene therapy trials are the number of expressing cells and the level of CFTR expression which must be attained to provide clinical benefit. In agreement with the observation of low levels of CFTR in some normal individuals[55], experiments using tissue culture assays[56] and administration to nasal epithelia[52] have indicated that relatively low levels of CFTR expression may provide benefit. The conclusive answer for what level of expression is required for therapeutic correction of the lung defect will only be achieved from actual clinical trials. In addition, the consequences of heterologous expression of CFTR, in cell types which normally do not express it are not clear, although studies on animals have not shown a deleterious effect upon heterologous expression of CFTR in the lungs[48].

The earliest gene transfer strategies aimed at the respiratory epithelium took advantage of the high efficiency and natural tropism of the common cold virus (adenovirus)[57]. To act as a gene transfer vehicle, the virus was modified by removal of a portion of its genome which codes for genes expressed early in the infectious cycle. This viral engineering was to prevent the spread of adenovirus infection as well as to enable the insertion of heterologous minigenes. The capability of the recombinant virus containing the CFTR minigene to exist in an episomal state within cells (not incorporating into the genome) and its ability to readily infect the lung epithelium made it an obvious choice for the initial gene transfer trials. The early experiments with this virus were aimed primarily at establishing its optimum dosage in clinical trials by determining its maximum efficiency at negligible toxicity. Although it was shown that this strategy did successfully correct the CF-associated anion defect both *in vitro*[56] and *in vivo*[52] with relatively high efficiency, its transient nature required chronic administration. Multiple administrations of the virus were not tolerated due to an immunogenic response against the viral proteins[51,58]. A second generation adenovirus-derived gene transfer vector contains a further change in its genome which prevents the expression of additional viral genes under certain conditions[59]. This vector has been shown to result in a decreased immunogenic response upon infection of CF respiratory tissue as compared with the first adenovirus vector and offers additional hope.

A related vehicle for gene transfer being refined is the adenovirus associated vector (AAV)[60,61]. These vectors lack the adenovirus coding sequences and thus require assistance for packaging into viral paricles by helper viruses. These AAV vectors present several advantages over their precursor, including the ability to undergo site-specific integration into the human genome, and thus become stable entities alleviating the need for chronic administration. Other advantages of these vectors include minimal pathogenicity and high transfer efficiency to the respiratory epithelia. Potential disadvantages of this vector include inefficient production of the vector and the relatively small capacity for incorporation of recombinant sequences such as the CFTR minigene. Nevertheless, these vectors have proven their ability to stably transfer the CFTR minigene[62]. With the rapid advances occuring in this field, the different shortcomings of the AAV system may soon be resolved.

An alternative vehicle being considered for genetic therapy is the liposome-DNA complex[63]. Liposomes are cationic lipid molecules which readily bind DNA. The hydrophobic nature of the lipid moeity enables the DNA-liposome complex to easily enter cells and deposit its bound DNA. This approach offers the advantage of no administration of foreign proteins, therefore potentially alleviating the immunogenic response. The disadvantage of liposome-mediated gene transfers is primarily inconsistent expression *in vivo* as compared with the adeno-vectors. Even with this potential disadvantage, administration of liposome-DNA complexes to the airways by aerosolization or instillation has demonstrated relatively high efficiency of gene delivery to the epithelia with no observable toxicity[64,65]. Correction of the pulmonary anion conductance defect in CF mice has also been transiently corrected with liposome-CFTR DNA complexes[49] offering further promise for this gene transfer vehicle.

A relative newcomer into the gene therapy field are vectors utilizing DNA-ligand complexes[66]. These vehicles utilize a receptor ligand which is specific for a certain cell type bound to a cationic molecule such as polylysine which binds DNA non-covalently. The major advantage of this system is its ability to potentially target specific tissues or cell types and be internalized by its cognate receptor.

Although the early trials with CFTR gene tranfers have been hailed as a relatively successful initial venture, much is still unknown, and may have been oversimplified. The initial boundary for efficient gene transfer by way of the airways is the mucus layer, which in severely affected CF patients may prove to be rather ominous. It is possible that this barrier may prevent efficient transfer of the therapeautic agent, therefore decreasing the efficiency of airway delivery and necessitating a vascular route. In addition, studies of endogenous gene expression of human lung tissue demonstrates CFTR expression in the respiratory epithelia, but the predominent site of expression is observed in the sub-mucosal glands which may not be readily accessible through airway luminal administration. Can the correction of the chloride channel defect predominantly in the epithelial cells suffice, or is correction of the sub-mucosal glands also required? A recent study of CFTR gene therapy on the nasal epithelia of a CF mouse model[67] has demonstrated a partial correction of the anion transport defect in these mice, but no apparent amelioration of the sodium hyperabsorption abnormality. Although the reason for this apparent discordancy is not known, inadequate or mistargeted transfer of the CFTR minigene has been suggested as an explanation. Furthermore, the imminent heterologous expression of the CFTR protein through non-specific application to the lung tissue may result in as yet unknown deleterious consequences; although no such adverse effects have yet been noted in animal and clinical trials, long term effects with chronic applications are unknown. The next concern is with immunogenic responses. Since current generation gene transfer vectors are transient in nature, chronic administration of the therapeutic agent is required. The multiple introduction of foreign proteins via adenoviruses may actually compound the problems of CF by the initiation or acceleration of an immunogenic response against the lung tissue containing the foreign protein. In addition, the expression of a wild-type CFTR protein in CF individuals which have not presented this protein may itself result in immunogenicity. Furthermore, although the pri-

mary function of CFTR may be chloride channel related, the possible presence of secondary functions of discrete CFTR proteins through alternative splicing is not fully understood.

Answers to the various questions will eventually be answered through clinical trials on CF patients. The future of successful genetic based therapeutic interventions may be far different from the relatively primitive attempts of today. Although much has been accomplished the major advances are yet to come.

References

1. Rosenstein BJ, Langbaum TS. Diagnosis. in Cystic Fibrosis (ed. Taussig, L.M.) 85-114. Thieme-Stratton, New York, 1984.
2. Taussig LM, Landau LI, Marks MI. Respiratory system. in Cystic Fibrosis (ed. Taussig, L.M.) 115-174. Thieme-Stratton, New York, 1984.
3. Mearns MB, Hunt GH and Rushworth R. Bacterial flora of the respiratory tract in patients with cystic fibrosis 1950-1971. Arch Dis Child 1972; 47: 902-907.
4. Stern RC, Boat TF, Wood RE, Matthews LW and Doershuk CF. Treatment and prognosis of nasal polyps in cystic fibrosis. Am J Dis Child 1982; 136: 1067-1070.
5. di Sant'Agnese PA, Darling RC. Abnormal composition of sweat in cystic fibrosis of the pancreas. Clinical significance and relationship to the disease. Pediatrics 1953; 12: 549-563.
6. Schwartz RH and Milner MR. Other manifestations and organ involvement. in Cystic Fibrosis (ed. Taussig, L.M.) 398-400. Thieme-Stratton, New York, 1984.
7. di Sant'Agnese PA and Hubbard V. The pancreas. in Cystic Fibrosis (ed. Taussig, L.M.) 230-295. Thieme-Stratton, New York, 1984.
8. Hadorn B, Johansen PG and Anderson CM. Pancreozymin secretion test of exocrine pancreatic function in cystic fibrosis and the significance of the result for the pathogenesis of the disease. Aust Paediatr J 1968; 4: 8-22.
9. Oppenheimer E and Esterly JR. Cystic fibrosis of the pancreas. Morphological findings in infants with and without pancreatic lesions. Arch Pathol 1973; 96: 149-154.
10. Scorza A, Conti-Nibali S, Sferlazzas C, Saitta G and Tedeschi A. Ranitidine in children with peptic ulcer and patients with pancreatic cystic fibrosis. Intl J Clin Pharmacol Res 1990; 10: 179-182.
11. Finkelstein SM, Wielinski CL, Elliot GR, Warwick WJ, Barbosa J, Wu SC and Klein DJ. Diabetes mellitus associated with cystic fibrosis. J Pediatr 1988; 112: 373-377.
12. Farber S. The relationship of pancreatic achylia to meconium ileus. J Pediatr 1944; 24: 387-392.
13. Park RG and Grand RJ. Gastrointestinal manifestations of cystic fibrosis. A review. Gastroenterology 1981; 81: 1143-1161.
14. Hodson ME, Mearns MB, and Batten JC. Meconium ileus equivalent in adults with cystic fibrosis of the pancreas. A report of six cases. Br Med J 1976; 2: 790-791.
15. Stern RC, Izant RJ, Boat TF, Wood RE, Matthews LW, and Doershuk CF. Treatment and prognosis of rectal prolapse in cystic fibrosis. Gastroenterology 1982; 82: 707-710.
16. Farber S. Pancreatic insufficiency and the coeliac syndrome. N Engl J Med 1943; 229: 653-682.
17. Tanner MS. Liver and biliary problems in cystic fibrosis. J Roy Soc Med Supplement 19 1992; 85: 20-24.
18. Brugman SM and Taussig LM. The reproductive system. in Cystic Fibrosis (ed. Taussig, L.M.) 323-337. Thieme-Stratton, New York, 1984.
19. Rommens JM, Ianuzzi MC, Kerem B-S, Drumm ML, Melmer G, Dean M, Rozmahel R, Cole JL, Kennedy D, Hidaka N, Zsiga M, Buchwald M, Riordan JR, Tsui L-C and Collins FS. Identification of the cystic fibrosis gene: Chromosome walking and jumping. Science 1989; 245: 1059-1065.
20. Riordan JR, Rommens JM, Kerem B-S, Alon N, Rozmahel R, Grzelczak Z, Zielenski J, Lok S, Plavsic N, Chou J-L, Drumm ML, Ianuzzi MC, Collins FS and Tsui L-C. Identification of the cystic fibrosis gene: Cloning and characterization of complementary DNA. Science 1989; 245: 1066-1073.
21. Trezise AEO and Buchwald M. In vivo cell-specific expression of the cystic fibrosis transmembrane conductance regulator. Nature 1991; 353: 434-437.
22. Tizzano EF, Chitayat D and Buchwald M. Cell-specific localization of CFTR mRNA shows developmentally regulated expression in human fetal tissues. Human Molecular Genetics 1993; 2: 219-224.
23. Drumm ML, Pope HA, Cliff WH, Rommens JM, Marvin SA, Tsui L-C, Collins FS, Frizzell RA and Wilson JM. Correction of the cystic fibrosis defect in vitro by retrovirus-mediated gene transfer. Cell 1990; 62: 1227-1233.
24. Anderson MP, Rich DP, Gregory RJ, Smith AE and Welsh MJ. Generation of cAMP-activated chloride currents by expression of CFTR. Science 1991; 251: 679-682.
25. Tilly BC, Winter MC, Ostedgaard LS, O'Riordan C, Smith AE and Welsh MJ. cAMP-dependant protein kinase activation of CFTR chloride channels in planar lipid bilayers. J Biol Chem 1992; 267: 9470-9473.
26. Cheng SH, Rich DP, Marshall J, Gregory RJ, Welsh MJ and Smith AE. Phosphorylation of the R domain by cAMP-dependant protein kinase regulates the CFTR chloride channel. Cell 1991; 66: 1027-1036.
27. Quinton PM and Reddy MM. Control of CFTR chloride conductance by ATP levels through non-hydrolytic binding. Science 1992; 360: 79-81.
28. Barasch J, Kiss B, Prince A, Saiman L, Gruenert D and al-Awqati Q. Defective acidification of intracellular organelles in cystic fibrosis. Nature 1991; 352: 70-73.
29. Bradbury NA, Jilling T, Berta G, Sorscher EJ, Bridges RJ and Kirk KL. Regulation of plasma membrane recycling by CFTR. Science 1992; 256: 530-532.
30. Boucher RC, Stutts MJ, Knowles MR, Cantley L and Gatzy JT. Na+ transport in cystic fibrosis respiratory epithelia: abnormal basal rate and response to adenylate cyclase activation. J. Clin. Invest. 1986; 78: 1245-1252.
31. Tsui L-C. The spectrum of cystic fibrosis mutations. Trend in Genetics 192; 392-398.
32. Kerem B-S, Rommens JM, Buchanan JA, Markiewicz D, Cox TK, Chakravarti A, Buchwald M and Tsui L-C. Identification of the cystic fibrosis gene: genetic analysis. Science 1989; 245: 1073-1080.
33. Corey M, Durie P, Moore D, Forstner GG and Levison H. Familial concordance of pancreatic function in cystic fibrosis. J. Pediatrics 1989; 115: 274-279.
34. Kristidis P, Bozon D, Corey M, Markiewicz D, Rommens J, Tsui L-C and Durie P. Genetic determination of exocrine pancreatic function in cystic fibrosis. Am. J Hum. Genet. 1992; 50: 1178-1184.
35. Kerem B-S, Zielenski J, Markiewicz D, Bozon D, Gazit E, Yahav J, Kennedy D, Riordan JR, Collins FS, Rommens JM and L-C Tsui. Identification of mutations in regions corresponding to the two putative nucleotide (ATP)-binding folds of the cystic fibrosis gene. Proc Natl Acad Sci USA 1990; 87: 8447-8451.
36. Dean M, White MB, Amos J, Gerrard B, Stewart C, Khaw KT and Leppert M. Multiple mutations in highly conserved residues are found in mildly affected cystic fibrosis patients. Cell 1990; 61: 863-870.
37. Gasparini P, Nunes V, Savoia A, Dognini M, Morral N, Gaona A, Bonizzato A, Chillon M, Sangiuolo F, Novelli G, Dallapiccola B, Pignatti PF and Estivill X. The search for Southern European cystic fibrosis mutations: Identification of two new mutations, four variants, and intron sequences. Genomics 1991; 10: 193-200.
38. Sheppard DN, Rich DP, Ostedgaard LS, Gregory RJ, Smith AE and Welsh MJ. Mutations in CFTR associated with mild disease form Cl-channels with altered pore properties. Nature 1993; 362: 160-164.
39. Kerem E, Corey M, Kerem B-S, Rommens J, Markiewicz D, Levison H, Tsui L-C and Durie P. The relation between genotype and phenotype in cystic fibrosis - analysis of the most common mutation (DF508). N Engl J Med 1990; 323: 1517-1522.

40. Snouwaert JN, Brigman KK, Latour AM, Malouf NN, Boucher RC, Smithies O and Koller BH. An animal model for cystic fibrosis made by gene targeting. Science 1992; 257: 1083-1088.
41. Clarke LL, Grubb BR, Gabriel SE, Smithies O, Koller BH and Boucher RC. Defective epithelial chloride transport in a gene-targeted mouse model of cystic fibrosis. Science 1992; 257: 1125-1128.
42. Gabriel SE, Brigman KN, Koller BH, Boucher RC and Stutts MJ. Cystic fibrosis heterozygous resistance to cholera toxin in the cystic fibrosis mouse model. Science 1994; 266: 107-109.
43. Clarke LL, Grubb BR, Yankaskas JR, Cotton CU, McKenzie A and Boucher RC. Relationship of a non-cystic fibrosis transmembrane conductance regulator-mediated chloride conductance to organ-level in CFTR (-/-) mice. Proc. Natl. Acad. Sci. USA 1994; 91: 479-483.
44. Knowles MR, Clarke LL and Boucher RC. Extracellular ATP and UTP induce chloride secretion in nasal epithelia of cystic fibrosis patients and normal subjects in vivo. Chest 1992; 101(3 Suppl): 60S-63S.
45. Knowles MR, Church NL, Waltner WE, Yankaskas JR, Gilligan P, King M, Edwards LJ, Helms RW and Bourcher RC. Aerosolized amiloride as treatment of cystic fibrosis lung disease: a pilot study, Adv. Exp. Med. Biol. 1991; 290: 119-128.
46. Shak S, Capon DJ, Hellmiss R, Marsters SA and Baker CL. Recombinant human DNase I reduces the viscosity of cystic fibrosis sputum. Proc. Natl. Acad. Sci. USA 1990; 87: 9188-9192.
47. Drumm ML, Pope HA, Cliff WH, Rommens JM, Marvin SA, Tsui L-C, Collins FS, Frizzell RA and Wilson JM. Correction of the cystic fibrosis defect in vitro by retrovirus-mediated gene transfer. Cell 1990; 62: 1227-1233.
48. Whitsett JA, Dey CR, Stripp BR, Wikenheiser KA, Clarke JC, Wert SE, Gregory RJ, Smith AE, Cohn JA, Wilson JM and Engelhardt J. Human cystic fibrosis transmembrane conductance regulator directed to respiratory epithelial cells of transgenic mice. Nature Genetics 1992; 2: 13-20.
49. Hyde SC, Gill DR Higgins CF and Trezise AEO. Correction of the ion transport defect in cystic fibrosis transgenic mice by gene therapy. Nature 1993; 362: 250-255.
50. Engelhardt JF, Yang Y, Stratford-Perricaudet LD, Allen ED, Kozarsky K, Perricaudet M, Yankaskas JR and Wilson JM. Direct gene transfer of human CFTR into human bronchial epithelia of xenografts with E1-deleted adenoviruses. Nature Genetics 1993; 4: 27-34.
51. Zabner J, Petersen DM, Puga AP, Graham SM, Couture LA, Keyes LD, Lukason MJ, St. George JA, Gregory RJ, Smith AE and Welsh MJ. Safety and efficacy of repetitive adenovirus-mediated transfer of CFTR cDNA to airway epithelia of primates and cotton rats. Nature Genetics 1994; 6: 75-83.
52. Zabner J, Couture LA, Gregory RJ, Graham SM, Smith AE and Welsh MJ. Adenovirus-mediated gene transfer transiently corrects the chloride transport defect in nasal epithelia of patients with cystic fibrosis. Cell 1993; 75: 207-216.
53. Wilson JM, Engelhardt JF, Grossman M, Simon RH and Yang Y. Gene therapy of cystic fibrosis lung disease using E1 deleted adenoviruses: a phase I trial. Hum. Gene Ther. 1994; 5: 501-519.
54. Engelhardt JF, Yankaskas JR, Ernst SA, Yang Y, Marino CR, Boucher RC, Cohn JA and Wilson JM. Submucosal glands are the predominant site of CFTR expression in the human bronchus. Nature Genetics 1992; 2: 240-247.
55. Chu CS, Trapnell BC, Curristin SM, Cutting GR and Crystal RG. Extensive posttranscriptional deletion of the coding sequences for part of nucleotide-binding fold 1 in respiratory epithelial mRNA transcripts of the cystic fibrosis transmembrane conductance regulator gene is not associated with the clinical manifestations of cystic fibrosis. J. Clin. Invest. 1992; 90: 785.
56. Zabner J, Couture LA, Smith AE and Welsh MJ. Correction of cAMP-stimulated fluid secretion in cystic fibrosis airway epithelia: efficiency of adenovirus-mediated gene transfer in vitro. Hum. Gene Ther. 1994; 5: 585-593.
57. Kozarsky KF and Wilson JM. Gene therapy: adenovirus vectors. Curr. Opin. Genet. Dev. 1993; 3: 499-503.
58. Yei S, Mittereder N, Wert S, Whitsett JA, Wilmott RW and Trapnell BC. In vivo evaluation of the safety of adenovirus-mediated transfer of the human cystic fibrosis transmembrane conductance regulator cDNA to the lung. Hum. Gene Ther. 1994; 5: 731-743.
59. Engelhardt JF, Ye X, Doranz B and Wilson JM. Ablation of E2A in recombinant adenoviruses improves transgene persistence and decreases inflammatory response in mouse liver. Proc. Natl. Acad. Sci. USA 1994; 91: 6196-6200.
60. Flotte TR. Prospects for virus-based gene therapy for cystic fibrosis. J. Bioenerg. Biomembr. 1993; 25: 37-42.
61. Nahreini P, Woody MJ, Zhou SZ and Srivastava A. Versatile adeno-associated virus 2-based vectors for constructing recombinant virions. Gene 1993; 124: 257-262.
62. Flotte TR, Afione SA, Conrad C, McGrath SA, Solow R, Oka H, Zeitlin PL, Guggino WB and Carter BJ. Stable in vivo expression of the cystic fibrosis transmembrane conductance regulator with an adeno-associated virus vector. Proc. Natl. Acad. Sci. USA 1993; 90: 10613-10617.
63. Hug P and Sleight RG. Liposomes for the transformation of eukaryotic cells. Biochim. Biophys. Acta. 1991; 1097: 1-17.
64. Stribling R, Brunette E, Liggitt D, Gaensler K and Debs R. Aerosol gene delivery in vivo. Proc. Natl. Acad. Sci. USA 1992; 89: 11277-11281.
65. Yoshimura K, Rosenfeld MA, Nakamura H, Scherer EM, Pavirani A, Lecocq J-P and Crystal RG. Expression of the human cystic fibrosis transmembrane conductance regulator gene in the mouse lung after in vivo intratracheal plasmid-mediated gene transfer. Nucl. Acids Res. 1992; 20: 3233-3240.
66. Cotten M, Wagner E and Birnstiel ML. Receptor-mediated transport of DNA into eukaryotic cells. Methods Enzymol. 1993; 217: 618-644.
67. Grubb BR, Pickles RJ, Ye H, Yankaskas JR, Vick RN, Engelhardt JF, Wilson JM, Johnson LG and Boucher RC. Inefficient gene transfer by adenovirus vector to cystic fibrosis airway epithelia of mice and humans. Nature 1994; 371: 802-806.

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Extralobar Pulmonary Sequestration and Associated Diaphragmatic Hernia

Rakesh Suri, BSc, 9T5

Abstract

Aberration in the process of fetal lung development is thought to be central to the pathogenesis of two fetal abnormalities often found in close association, congenital diaphragmatic hernia and extralobar pulmonary sequestration. The delivery of a child after an uncomplicated pregnancy and peripartum period is met with clinical deterioration and immediate respiratory distress of the neonate. A case is presented where the prenatal diagnosis of a neonate with this scenario is outlined, along with the subsequent postnatal stabilisation and surgical management at the Hospital for Sick Children in Toronto. A definition of the pathology, pathogenesis, clinical presentation, diagnosis and management of these conditions separately and in association is discussed. A commonly suggested theory for the combined pathogenesis is also presented. Refinement in the technology of prenatal ultrasonic diagnosis as well as evolving theories and techniques of in-utero fetal surgery will be a future frontier for the early rectification of pulmonary development in this condition.

Introduction

The process of fetal lung development is one which, to this day, has not been mastered by scientific understanding of its intricacies. Many theories have been propounded and the debate continues over the exact sequence of events as well as the nature of requirements necessary to allow the correct interaction between mesodermal and endodermal components in the embryo[1]. Furthermore, elucidation of this process is not only important for the sake of intervening to prevent the pathological processes themselves in utero, but also learning to clinically recognize these scenarios and avoid delays in management which often lead to fatal consequences post-natally. New technology holds promise here in three main areas: 1) radiological investigations, particularly ultrasound, to diagnose fatal lung malformations prenatally, 2) surgical intervention to correct lung abnormalities early in the peripartum period and 3) new techniques emerging in the field of fetal surgery to correct anomalies in utero and thus allow some salvaging of normal prenatal development[2]. The interaction of aberrant pulmonary development and these particular technological modalities can be demonstrated in a rare but previously reported phenomenon: that of extralobar pulmonary sequestration and associated diaphragmatic hernia. The presentation, diagnosis, management and pathogenesis of these associated conditions will be discussed in the example of a neonate presenting to the Hospital for Sick Children.

DINO PULERA

Case Report

The following case was seen at the Hospital for Sick Children(HSC) in Toronto, Ontario in June of 1994. A few hour old infant was transferred to the HSC, intubated due to respiratory distress at birth. Pregnancy history was non-contributory and included no occurrence of gestational diabetes, no hypertension and no polyhydramnios. The pregnancy had been followed by a midwife and had been assigned an expected date of confinement which was two weeks previous to

the actual delivery. An ultrasound done the day before delivery (42 wks) revealed the presence of a congenital diaphragmatic hernia on the left side but no other congenital anomalies. The patient was born to a 30 year old G1 female after prostin induction at 42 weeks gestation. Vaginal delivery was assisted with mid-forceps and no meconium was found. The infant was immediately discovered to be in respiratory distress on delivery and was given apgars of 3 at 1 minute, 4 at 5 minutes and 5 at 10 minutes. Initial blood gases revealed a pH of 7, pCO_2 of 91, pO_2 of 17, HCO_3 of 27 and a base excess of -12. The patient was intubated at 2 minutes, a peripheral IV was inserted and fluid resuscitation was initiated with D10W 12 cc/hr, 5 meq bicarbonate, morphine 20 mg/kg/min and dopamine at 15 meq/kg/min.

Course in Hospital

The patient was admitted to the Pediatric ICU. Heart rate was 170, blood pressure 71/45 mm Hg, O_2 saturation 85-94% preductally and 75-80% postductally. Examination revealed decreased air entry into both lung fields. Cardiac auscultation demonstrated a normal S1 and S2 with a patent ductus murmur and good peripheral perfusion with normal peripheral pulses. Abdominal examination found no organomegaly. Blood gases included a pH of 7.42, pO_2 38, CO_2 34 and HCO_3 24. Chest x-ray revealed a left diaphragmatic hernia and a right pneumothorax (Figure 1). Ventilator settings were 30/4, FiO_2 100% and rate of 60. A right sided chest tube was inserted. The patient was stabilized and maintained in PICU. She was taken to the operating room three days later. A right subcostal incision was used to gain exposure to the diaphragmatic defect. In it was the right lobe of the liver, and most of the small bowel, colon, spleen and stomach. These organs were removed from the chest and replaced in the abdomen. Subsequently, a large cystic mass was noted to arise from the fundus of the stomach which was later identified to be a gastric duplication cyst. Inspection of the chest revealed a moderately sized lung with a left lower extralobar sequestration that had vascular attachment to the aorta and had no connection to normal lung. Furthermore, the sequestration was enveloped in a separate pleural sac. Vessels to the sequestration were ligated with silk and the diaphragmatic defect was repaired with interrupted 3-0 mattress Vicryl sutures and transverse sutures were utilized to appose thinner attenuated areas of the defect. Satisfactory closure of the diaphragmatic hernia was felt to be achieved and the chest was closed without insertion of a chest tube. Additionally, the gastric duplication cyst was dissected free of the gastric serosa and drained clear fluid on removal. The gastric defect was closed with continuous running 3-0 Vicryl sutures. Ensuring that the spleen was in the left upper quadrant and that the intestines were placed appropriately, the abdomen was closed with continuous running 2-0 Dexon in two layers and skin clips superficially. A butterfly needle was inserted into the right chest anteriorly under water seal. The patient was then transported back to the PICU intubated and was ventilated in excellent clinical condition.

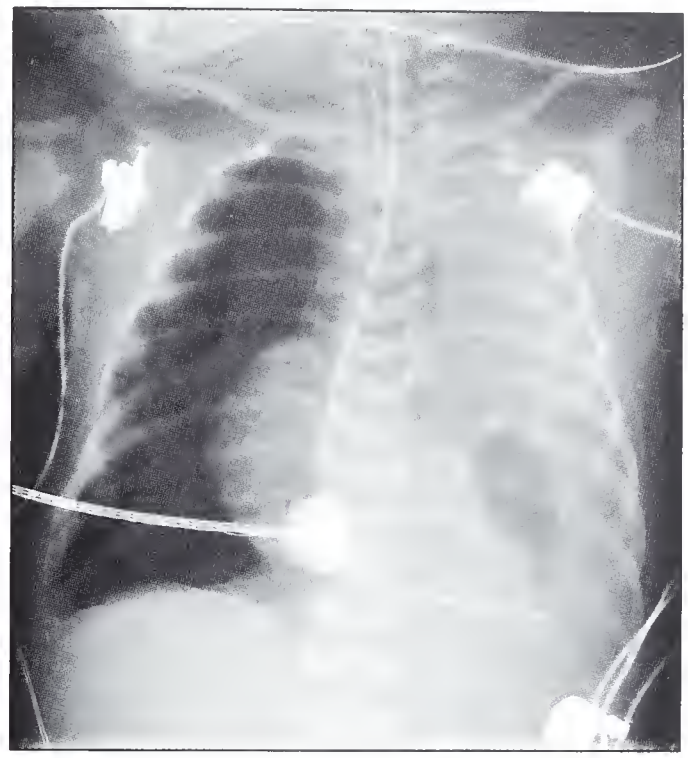


Figure 1: Chest x-ray showing a left diaphragmatic hernia and a right pneumothorax.

Subsequent pathological examination of the sequestration revealed a mass measuring 3.9 x 2.7 x 1.3 cm. A dark blue color was prominent uniformly beneath the pleural surface. Sections revealed lung parenchyma encased in visceral pleural cells. The hilum of the mass was found to contain an elastic artery. Actual parenchymal material demonstrated redundant ciliated columnar epithelium-lined bronchioles and congestion throughout. Airways were found to be dilated, were circumscribed by smooth muscle and contained inspissated mucus plugs. Alveolar spaces were filled with macrophages and the interstitium contained a mild mononuclear infiltrate.

The patient's clinical course steadily improved and led to extubation seven days postoperatively. An echocardiogram performed on the patient revealed bidirectional shunting across a patent ductus arteriosus. One period of re-intubation was required for several days during which the patient underwent surgery for patent ductus ligation. From this point the patient steadily improved and left hospital against medical advice after a total of thirty-four days in hospital. The only concern at this time was her slow weight gain. She was followed up in out patient clinic eight days later and was found to be progressing well.

Discussion

Congenital diaphragmatic hernias are quite uncommon at 1/2200 live births[4]. They arise at about 8-10 weeks gestation due to a lack of closure of the pleuroperitoneal canal before bowel returns to the abdomen. Two predictable factors regarding this condition are that they are often unilateral and these are often on the left

side. Tragically the scenario is frequently accompanied by a 75% fatality rate despite postnatal intervention[2]. Investigation of a pregnancy which is large for dates because of polyhydramnios results in prenatal diagnosis. Ultrasound can often confirm this by viewing fluid filled intestinal loops or stomach in the chest as well as the absence of a gastric bubble in the left upper quadrant. In severe cases, where more bowel is present in the thorax, mediastinal shift can lead to bilateral pulmonary hypoplasia and hydrops; both of which have associated mortalities approaching 100%[4]. Pulmonary hypoplasia is defined by a decreased amount of lung tissue for gestational age or birth weight. Severe cases cause the neonate to present with signs of respiratory distress and difficulty with ventilation. Other anomalies which can often accompany this scenario include interstitial emphysema, pneumothorax, pneumomediastinum, pneumopericardium and persistent fetal circulation[2].

Histological examination of hypoplastic lung arising from this condition reveals retarded development of elastic fibres in the existing parenchymal framework when compared with age matched normally developed lungs[5].

On delivery of an infant with pulmonary hypoplasia due to congenital diaphragmatic hernia, the need for treatment is acute and essential. A two fold approach has been successful in salvaging some lives where pulmonary hypoplasia is not severe. Firstly, pulmonary support must be initiated using high frequency ventilation or extracorporeal membrane oxygenation and secondly, surgical intervention must be utilized to reduce the herniated bowel and repair the diaphragm.

Pulmonary sequestration is included under the grouping of Bronchopulmonary Foregut Malformations proposed by Gerle et al., and is thought to represent one position in a spectrum of anomalies arising due to aberrant development of the embryonic lung buds and foregut[2]. Sequestration of lung is a congenital malformation which causes the development of pulmonic tissue which is unattached to the tracheobronchial system or pulmonary arteries. Rather, this anomalous island of autonomous lung parenchyma is supplied by arteries from the abdominal or thoracic aorta. There are two categories of such malformations, intra- and extralobar sequestrations. Extralobar sequestrations are the less prevalent of the two(25%)[6] in all age groups taken together. However an examination of its prevalence during the fetal and neonatal periods reveal that it is the most frequently found pulmonic sequestration in this time period[2]. It is characterized as an autonomous island of pulmonic tissue often found in the left hemithorax, as described above, encased in its own separate visceral pleural sac. Histological examination of such areas of lung tissue reveal the presence of branching bronchioles which are immature as well as dilated alveoli possessing a cuboidal epithelial lining. Elastic fibres however, are well developed[5]. Rarer variants may show islands of parenchyma in the abdomen, or associated with other mediastinal or chest wall structures. Furthermore, its venous drainage often runs to one of the following: the azygous/hemiazygous, the portal vein or the vena cava. A report by Smith suggests that 90% of extralobar sequestrations occur on the left side[10]. In addition, DeParedes et al. report that almost all cases of extralobar sequestration occur in the posterior costodiaphragmatic angle[3].

Diagnosis of this malformation occurs either prenatally or in the peripartum (61%), as the infant goes into early respiratory distress[6]. Acute distress arises due to 1) a secondary mass effect on the ipsilateral lung or the mediastinum, 2) congestive heart failure 3) an overload of the pulmonary circulation or 4) pulmonary hypoplasia due to associated congenital diaphragmatic hernia. Diagnosis of prenatal structural abnormalities and consequences on surrounding lung is not always helped by measurement of the Lecithin: Sphingomyelin ratio alone. Rather, routine real time sonography, even by the second trimester, has been found to be the most specific means of diagnosing malformations such as congenital diaphragmatic hernia and pulmonary sequestration[2,7]. Extralobar sequestrations are identified by discovery of a solid, hyperechoic mass. Confirmatory details include definition of feeding and draining vessels(although in utero, delineation of arterial and venous supplies by color Doppler may not be possible[2,7].) Associated conditions in utero include fetal hydrops, pulmonary effusion, polyhydramnios and diaphragmatic hernia. Review of the literature confirms that there is a greater than 50% association between extralobar sequestration and congenital diaphragmatic hernia[1,2,3,4,6,7,8].

According to DeParedes et al., clinical presentation of extralobar sequestration differs from intralobar sequestration in that 1) extralobar sequestration is more often present in males, 2) the age of diagnosis is less than one year in 59% and is often later in intralobar sequestrations, 3) there is a higher frequency of associated anomalies in extralobar sequestration, the most prevalent being congenital diaphragmatic hernia, 4) the most characteristic extralobar sequestration symptomatology includes respiratory distress with a noted association of other symptoms such as vomiting, feeding problems, respiratory infections and abdominal pain. Intralobar sequestration on the other hand, characteristically presents in the older child with a history of recurrent pulmonary infections[3]. Gerle et al., also report the presentation of a combined extralobar sequestration and congenital diaphragmatic hernia with hematemesis due to communication of a hemorrhagic sequestration with the stomach[8].

Several theories describing the embryologic origin of pulmonary sequestrations have been proposed.

Clements and Walker postulate the existence of an embryological insult, which interferes with the formation of the normal interconnections in developing lung parenchyma. This is thought to cause the anomalous connections, or "malinosculations", in the resultant sequestered parenchyma[9]. The only prevalent theory of embryologic etiology of the association between extralobar sequestration and congenital diaphragmatic hernia has been put forward by Wells[11]. The relationship is explained by the presence of an anomalous connection between the sequestration and the gastro-esophageal area. This large, anomalous mass is proposed to interfere with the closure of the medial margin of the pleuroperitoneal canal by blocking its movement towards the esophageal hiatus. Therefore, a patent canal results in the combined defect[11].

Diagnosis of sequestered lung parenchyma centers around the identification of certain components which define a position in the sequestration developmental spectrum. These include: 1) a sequestered or dysplastic lung mass, 2) anomalous arterial supply, 3) abnormal venous drainage, 4) bronchial or enteric communication, 5) gross lung abnormalities(eg. hypoplastic lung associated with congenital diaphragmatic hernia), and 6) diaphragmatic defects[7].

Postnatal investigations are therefore aimed at identifying these elements. These include: chest x-ray (CXR), which has characteristic findings and is key to diagnosis, CT scans for cases more difficult to interpret via CXR, Doppler ultrasonography for deineation of vascular connections and a barium swallow to identify communication between the sequestration and the gastrointestinal tract. Some authors feel that angiographic exploration of the sequestrated area is an essential preparatory step before surgical ligation can proceed[6]. However, the increasing availability of Magnetic Resonance Imaging seems to suggest this modality as a superior means of identifying parenchyma, vessels and other anomalous structures via a single imaging technique.

Definitive treatment of both types of lung sequestration is excision of the affected pulmonary parenchyma after ensuring identification and ligation of the feeding artery and subsequently, the draining vein[1]. Adjuncts to surgical treatment include preparatory medical treatment with agents to decrease pulmonary-systemic anastamosis as well as embolization of anomalous vessels in order to decrease intra-operative bleeding. Good prognostic factors for surgical intervention in neonates include the absence of pulmonary hypoplasia or hypertension, whereas all older children tend to do well with surgical intervention[1].

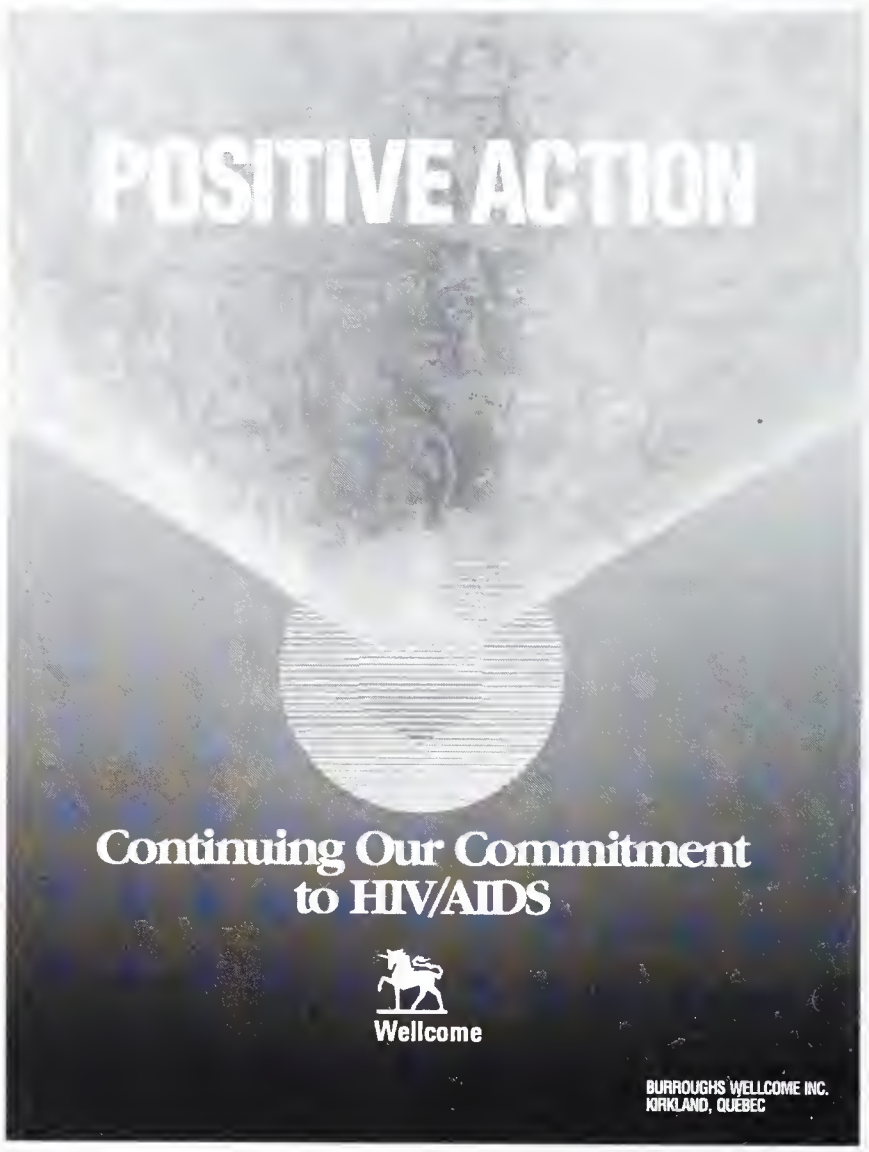
Prenatal surgical intervention to correct fetal abnormalities has largely been restricted to the treatment of specific conditions such as congenital diaphragmatic hernia, hydrocephalus and lower urological abnormalities and sacrococcygeal teratoma[12]. Entertaining the possibility of in-utero surgery for other conditions which cause space-occupying thoracic lesions, such as congenital cystic adenomatoid malformation of the lung, is becoming increasingly prevalent however[13]. The specific indications for intervention have been assessed through a multi-factorial risk assessment scheme which includes the size of the intrathoracic lesion as well as the presence of fetal hydrops along with other parameters of fetal well being and maternal risk[13]. The in-utero management of extralobar sequestration, particularly in association with congenital diaphragmatic hernia, has not been assessed in the literature. It is conceivable however that this same multi-factorial assessment of the appropriateness of in-utero intervention for fetal therapy, in order to allow the resumption of normal fetal pulmonary development, may be applicable to these two conditions in the future.

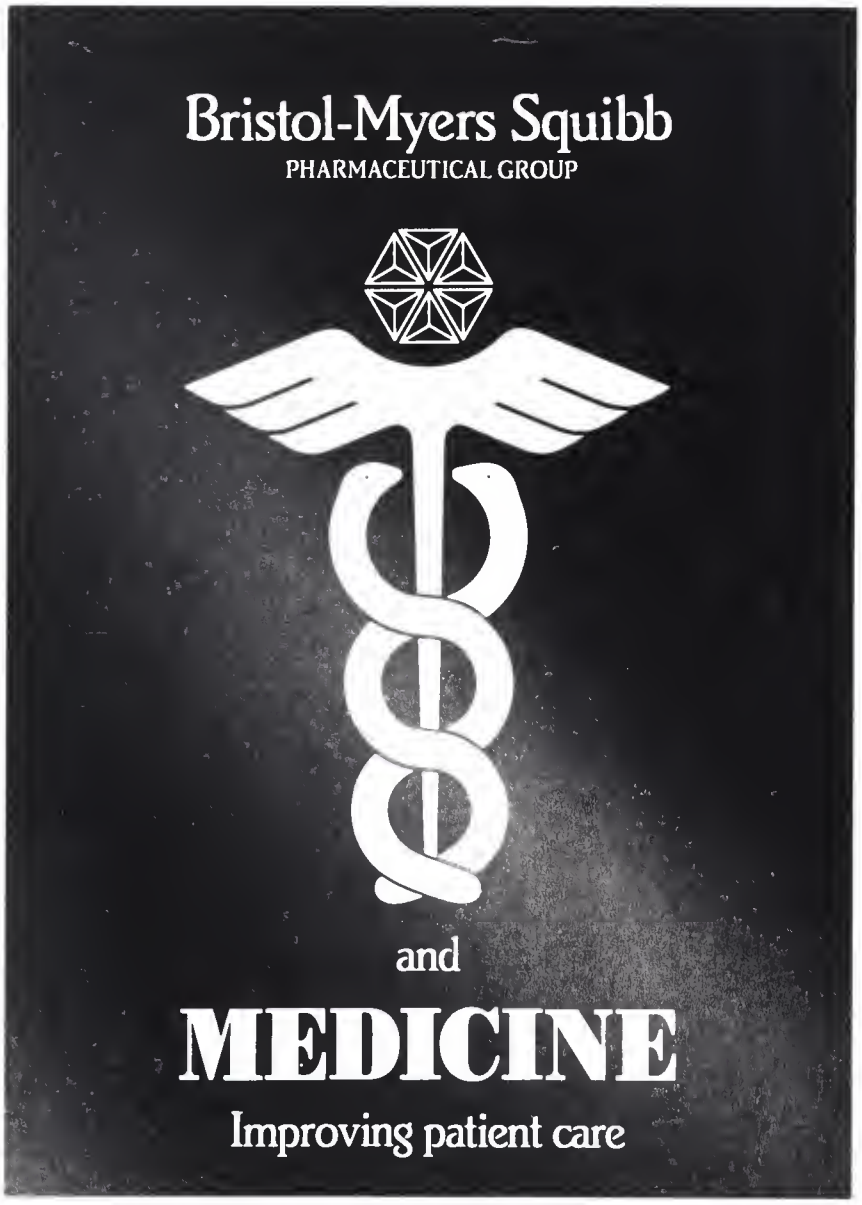
The presentation of a perinate in respiratory distress with two rare but commonly associated malformations, congenital diaphragmatic hernia and extralobar pulmonary sequestration, is a condition amenable to efficient prenatal diagnosis and definitive surgical management. Ever improving ultrasound investigation accords the physician the ability to identify such a scenario through routine screening and facilitates expectant surgical management after delivery or may even allow the consideration of in-utero surgical intervention to be held as a realistic means of managing this condition. Certainly, the latter option stands as the more favorable route for allowing subsequent pulmonary development to proceed unimpeded by either the sequestered parenchyma or the herniated abdominal contents. Future refinement of theories and techniques in fetal surgery along with the minimization of maternal risk will allow such a consideration to be commonplace; not only surgery for congenital diaphragmatic hernia and pulmonary sequestration, but also for a broad array of fetal developmental abnormalities.

References

1. Bailey P.V., Tracy T., Connors R.H., DeMello D., Lewis J.E., Weber T.R. Congenital Bronchopulmonary Malformations: Diagnostic and Therapeutic Considerations. J.Thorac Cardiovasc Surg 1990; 99: 597-603.
2. May DA, Barth RA, Yeager S, Nussbaum BA, Bulas DI. Perinatal and Postnatal Chest Sonography. Radiol Clin North Am 1993; 31(3): 499-516..
3. DeParedes CG, Pierce WS, Johnson DG, Waldhusen JA. Pulmonary Sequestration in Infants and Children: A 20-year Experience and Review of the Literature. J Pediat Surg 1970; 5(2): 136-148.
4. Sabiston DC, Textbook of Surgery, The Biological Basis of Modern Surgical Practice(14th Ed.). WB Saunders Co. 1991: 1163-1165.

5. Nakamura Y., Fukuda S., Hashimoto T. Pulmonary Elastic Fibers in Normal Human Development and In Pathologic Conditions. Pediatr Pathol 1990; 10(5): 689-706.
6. Felker RE, Tonkin LD. Imaging of Pulmonary Sequestration. American Journal of Radiology 1990; 154: 241-249.
7. Baumann H, Kirkinen P, Huch A. Prenatal Ultrasonographic Findings in Extralobar Subdiaphragmatic Lung Sequestration-a case report. J.Perinat. Med. 1988; 16: 67-69.
8. Gerle RD, Jaretzki A, Ashley CA, Berne AS. Congenital Bronchopulmonary-Foregut Malformations: Pulmonary Sequestration Communicating with the Gastrointestinal Tract. The New England Journal of Medicine 1968; 278(26): 1413-1419.
9. Clements BS, Warner JO. Pulmonary Sequestration and Related Congenital Bronchopulmonary-Vascular Malformations: nomenclature and classification based on anatomical and embryologic considerations. Thorax 1987; 42(6): 401-408.
10. Smith RA. Theory of Origin of Intralobar Sequestration. Thorax 1956; 11:10.
11. Wells LJ. Development of Human Diaphragm and Pleural Sacs. Embryology 1954; 35: 107-134.
12. Bargy F. Fetal Surgery: for what purpose? Pediatrie 1992; 47(5): 347-350.
13. Adzik NS, Harrison MR, Flake AW, Howell LJ, Golbus MS, Filly RA. Fetal Surgery for Cystic Adenomatoid Malformation of the Lung. Journal of Pediatric Surgery 1993; 28(6): 806-812.





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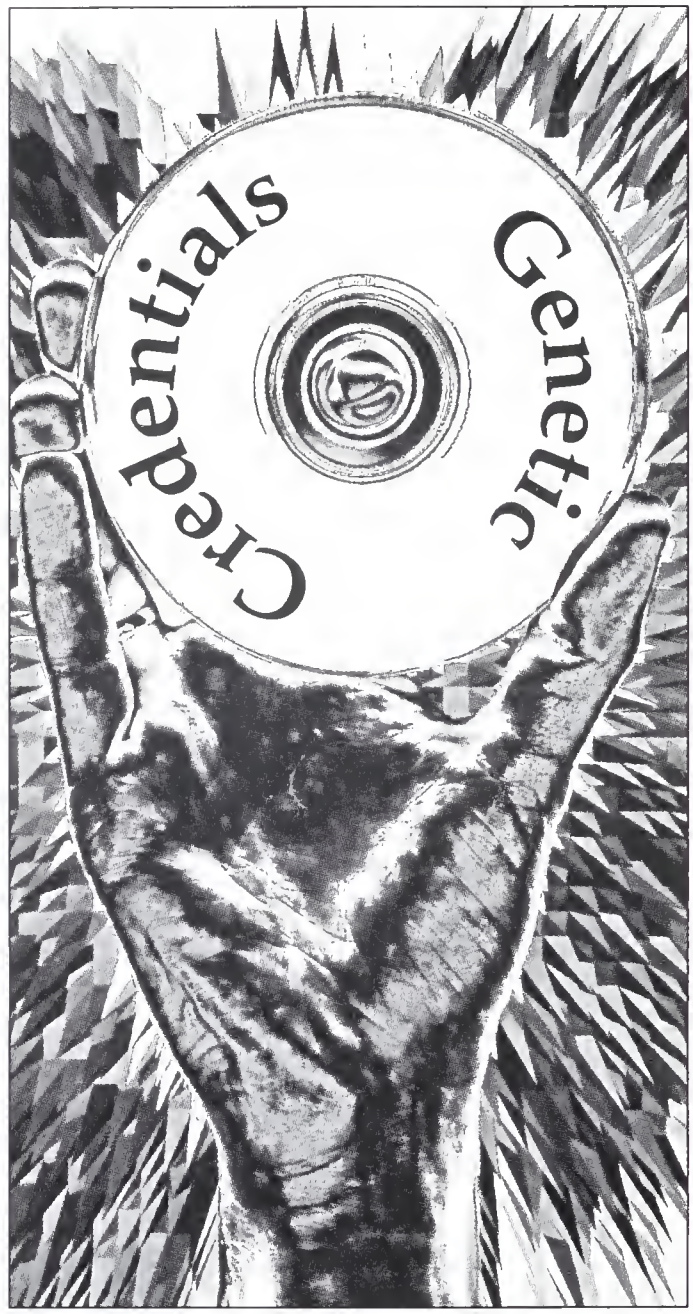
Genetic Testing in the Workplace: Impetus, Considerations, and Proposed Solutions

Tarang N. Sheth, BArtsSc 9T8

Abstract

The Human Genome Project is likely to provide the capability of knowing an individual's complete genetic profile. Such a profile would include not only information about serious disease traits but also about disease susceptibility and conditions of minor severity. The strong impetus for the introduction of these genetic tests into widespread use necessitates a careful examination of their implications, particularly in the workplace.

In this paper, genetic testing by employers is examined in three different contexts: identification of workers more susceptible to workplace hazards, identification of workers in jobs where the public's safety might be threatened by a genetically-influenced condition, and the use of genetic testing to select the healthiest workers. The questions posed by each of these uses of genetic testing are discussed and several regulatory strategies are considered.



BRYCE HOUGH

Introduction

The Human Genome project is a multinational effort to identify and sequence all the genes in the human body. As a more than three billion dollar enterprise, it is one of the largest scientific projects ever undertaken. Already genetic probes have been developed for a number of early-onset, dominant-allele genetic disorders. In addition, probes for recessive conditions such as thalassemia, cystic fibrosis and other recessive conditions are available. With continuing research, markers for conditions with complex multigenic and environmental etiology are likely to be found. Eventually, diagnostic tests may also be available for a genetic predisposition to behavioural conditions, such as schizophrenia and manic depressive disorder, as well as conditions of relatively minor severity such as obesity, freckling, myopia, and some learning disorders[1].

In the absence of prospective planning or proper regulation, these new genetic diagnostic tests may be rapidly introduced as medical services. There are strong forces driving this trend. The biotechnology industry has been very quick to develop commercial tests after a gene marker has been discovered[2]. There are clear financial incentives for companies to develop and market these tests, and moreover, for them to encourage genetic testing as a routine part of medical care delivery[1]. There is also pressure on professionals. Without clear clinical guidelines for the use of new technologies, medical practitioners are under the threat of litigation for failing to use available technology that is available[3]. Furthermore, patients and third parties are likely to find genetic tests of considerable interest.

The rapid rate at which genetic diagnostic capability is increasing and the strong forces for the development and introduction of commercial tests significantly enhance the need for discussion of relevant issues. In this paper, I examine the implication of genetic tests conducted by employers. In particular, I consider the impetus for the implementation of genetic tests, various ethical issues that arise, and regulatory solutions.

Impetus for Workplace Genetic Testing

The idea that knowledge of the different genetic constitutions of workers could be used to select those more suitable for employment is not a new one. In 1938, the geneticist J. B. S. Haldane observed that normal workers vary in the extent to which they become symptomatic after exposure to a particular occupational hazard. He postulated that the difference in response to toxic exposures was at least in part genetically determined. If the more susceptible individuals could be directed to other occupations, Haldane reasoned, the number of people with occupation-induced illness would decline[4].

Today, with the growing capability to diagnose susceptible people in the manner Haldane had conceived, the pressure for genetic testing of workers is increasingly intense. Genetic testing in the workplace is presently advocated for three reasons. The first, as Haldane suggested, is to reduce the risk to individual workers by not allowing genetically high-risk persons to work in a hazardous environment. Consider the following hypothetical scenario:

> *A chemical company manufactures a certain range of chemicals at one of their plants that, although manufactured under strict guidelines, entail an added risk of illness for their employees. Their department of human resources has noticed that workers at this plant have a 35% higher incidence of cancer than at other plants. The higher rate has translated into increased disability claims and the occasional law suit. The plant manager, an avid reader of the genetic testing trade magazines, finds out that a genetic test is available for a gene allele which increases an individual's risk for cancer when exposed to the type of chemicals his plant makes. Should such a test be implemented to identify high risk workers?*

In this case, the employer has a strong interest in identifying those who are more susceptible and removing them from the environment because it would lower the cost of worker disability and help avoid possible lawsuits based on management's responsibility[5]. Furthermore, if the company was based in the United States, testing would help protect the employer from the medical costs associated with worker illness[5].

The second use of genetic testing is on those who hold jobs that involve the safety of the public in general. Testing these individuals would allow the removal of those who, as a result of their genetic profile, appear to be at high-risk for a condition that could impair their ability to do their job properly and thus endanger the public's safety. Consider the following hypothetical scenario:

> *In light of the recent increase in sexual misconduct among physicians and studies that this is most likely due to an increasing prevalence of psychiatric illness among physicians, the Ontario government is implementing a novel approach to the problem. The Minister of Health has announced that all applicants to medical school will have to submit to a broad spectrum genetic test, to detect genetic predisposition to psychiatric illness. Any applicants testing positive for susceptibility will be excluded from the admissions process. Addressing the problem upstream, the Minister notes, should save the public considerable distress and proves that the government is doing all it can to protect the public's safety.*

In this case, an anticipated danger to the public's well-being is removed. The government's impetus, like any employer who controls the selection of those in public-safety sensitive occupations, is to weed out potentially harmful workers. In the case of a corporation, there is the additional incentive to avoid possible lawsuits from victims of the worker's deficit in performing the task[4].

The third impetus for genetic testing is to identify workers with the lowest genetically determined susceptibility to chronic diseases – disease which have no implication in the immediate work environment – and to use these results as criteria in hiring. Consider the following hypothetical case:

> *A large company spends large sums of money on the training the development of its top executives. From the outset of their careers, it incurs expenses that include paying for business school education, providing additional training opportunities, and investing company responsibilities in them, and paying their considerable salaries. Since loyalty to the company is high among executives, those selected initially to be executives remain to serve the company for their whole careers. Given the sizable investment the company makes in its future executives, The Board of Directors is presented with a proposal to screen all applicants to the executive training program for susceptibility to the common chronic diseases, such as heart disease and cancer. Should they go ahead with the idea?*

In this case, the company's objective is to hire only those who are most likely to remain healthy in the future. Such testing is advocated solely by employers, who stand to reduce losses due to worker illness. Benefits would include savings on disability insurance, on the cost of lost productivity from ill workers, and the cost of training replacement workers[4]. For prospective applicants, or the public there is no conceivable benefit.

Ethical Considerations

Each of these types of genetic testing raises important concerns. In the case of testing for high-risk employees in hazardous environments, the use of genetic testing alters conventional notions of occupational health. Traditionally, occupational health has been conceived of as improving the health of the worker by improving the conditions of work. In the case outlined, this means the chemical company takes every possible precaution to protect its workers.

As Rothman points out, genetic testing for high-risk individuals represents a different approach, in which the

health of the working population is maintained not by preventing the members of that population from becoming sick, but by keeping those most likely to get sick out of the working population[6]. The necessity for the company to identify and remove the remaining hazardous aspects of the worker's environment is decreased, because the screened worker population is less susceptible on the whole[3].

Moreover, if employers are allowed to hire and fire workers based on their high-risk then an important element of worker liberty and freedom would also be violated. Although the company might claim that it is doing those more susceptible a service by not hiring them, it would be paternalistic to assume that the worker would not want to live with the high-risk situation. Unless properly controlled, it is possible that a screening programme for high-risk employees in hazardous work environments, would likely serve the interests of the employer over the employees.

The testing of people in public-safety sensitive occupations also poses a significant dilemma. In this case, there is a conflict between an individual's right to privacy over his or her genetic constitution and the employer's interest in this information in order to prevent harm to the public[7]. This conflict is not easily resolved. Considering the example case, it is important to remember that prior to the availability of genetic testing, the public tolerated the risk of having doctors who were more predisposed to psychiatric illness and abuse of their patients. In addition, a positive genetic test will only indicate a predisposition to, but not the presence of, the actual condition. What will an extra 10% chance of a particular disease mean? How much extra risk is it? Interpreting the meaning of genetic tests for susceptibility in this context is quite problematic. It may not be fair to exclude someone from employment given this uncertainty. On the other hand, it may be suggested that any increased risk to the public's well-being is unacceptable. The collective interests of the public should perhaps override those of the prospective doctor. An appropriate resolution must address both issues.

The third type of genetic testing, which is an attempt to identify the healthiest individuals for prospective employment, is the most problematic. As indicated by the example, it is a markedly different use of testing than the previous two because it only serves the interests of the employer[8]. The selection of people based on their genetic profiles is a means for employers to avoid hiring those more likely to fall ill, for example, someone with a genetic predisposition to severe hypercholesterolemia. An individual's predictive genetic profile however, is beyond their control. Using this criteria in the hiring process, like in the other two cases, is discrimin-atory - but in this case there is no possible justification for the discrimination. It is foreseeable that widespread use could create a class of people deemed unemployable because they have a genetic risk of falling ill that no employer is willing to accept[9].

Proposed Solutions

Given these implications of genetic screening in the workplace, there are several regulatory measures that may be appropriate. In the case of high-risk workers in a hazardous work environment, genetic testing can complement traditional occupational health approaches, if it is carried out with strict safeguards to preserve equal employment opportunity[10]. 1) genetic testing should be forbidden before an offer of employment is made. This would ensure that employers don't implicitly use the results of the test in their hiring decisions, preventing employers from purposefully not hiring high-risk candidates[7]. 2) genetic testing should be completely voluntary. It should be the individual only who decides whether knowledge about his or her genetic makeup should be ascertained. Any coercive program in the workplace setting would be a violation of individual freedom and privacy. 3) the results of the test should be made available only to the worker. It is the individual affected who has the right to decide whether or not to accept the risks, not the employer. If the employer were denied access to test results, it would also ensure that the worker would not be subject to coercive pressure to leave[4]. Together these safeguards would ensure that the impetus for traditional occupational health measures is not lessened because the employer remains unaware of the employee's risk of disease. In the example case, the chemical company would arrange for workers, if they chose, to find out their risk. It would also leave the information confidential and allow the worker to make the decision to continue working or not. Thus, a carefully designed workplace genetic testing program can be a fair and responsible way to use the capabilities of genetic testing in this context.

In the case of testing to identify individuals who constitute a risk to public safety, genetic testing is not likely to be the best way to accomplish the goal of reducing the public's risk. Although the intentions of defending the public's interest are noble and may, in some people's opinion, justify the possible discrimination the test would entail, the value of the information that would be obtained is unclear. In addition, selectively targeting people who have a genetic predisposition to illness neglects other factors that can effect work performance. In the terms of the example case, not all doctors who abuse their patients have a psychiatric illness.

A better approach is one in which those who hold safety-sensitive jobs and those who work with them are counselled to recognize weaknesses in performances. Additional programs that help affected individuals deal with their difficulties would serve the public's interest and protect the privacy and rights of the individuals concerned[7]. This approach would also help identify those whose deficient performance is not predicted by a positive genetic test, and thus be fair to all individuals.

The third type of genetic testing, to screen for the healthiest workers, appears to serve only the interests of the employers and has no element of societal benefit. Using genetic tests to maximize the health of a workforce represents an inappropriate use of new genetic knowledge. It attempts to introduce a new form of discrimination into hiring decisions. Consequently, the most appropriate regulatory strategy is to prohibit the use of genetic testing for this purpose.

Conclusion

The capability to know more about our genetic endowment as a result of work on the Human Genome Project poses considerable ethical problems. This discussion has illuminated some of the pitfalls that can arise if this knowledge is used in several contexts in the workplace. Testing of workers in hazardous work environments can be beneficial if it is voluntary and confidential. Testing of individuals in occupations involving public safety is unlikely to be helpful, and the objective of protecting the public can be satisfied better by other means. The use of genetic testing to screen for the healthiest potential workforce serves only the employers' interest and represents a new form of discrimination in the hiring process.

As new issues arise in the use of genetic testing, consideration of the impetus and ethical implications of the testing can help clarify possible regulatory solutions for the use of genetic knowledge.

References

1. Nolan, Kathleen. First Fruits: Genetic Screening. Hasting Center Report 1992; 22(4): S2-S4.
2. Bishop, Jerry E and Michael Waldholz. Genome. New York: Simon and Schuster, 1990.
3. Rowley, Peter T. Genetic Screening: Marvel or Menace. Science. 1984; 225: 138-144.
4. Murray, Thomas H. Ethical issues in human genome research. FASEB J. 1991; 5:55-60.
5. Draper, Elaine. Genetic Secrets: Social Issues of Medical Screening in a Genetic Age. Hasting Center Report 1992; 22(4): S15-S11.
6. Rothman, Barbara Katz. Not All That Glitters is Gold. Hasting Center Report 1992; 22(4): S11-S15.
7. Orentlicher, David. Genetic Screening by Employers. Journal of the American Medical Association. 1990; 263: 1005,1008.
8. Kolata, Gina. Genetic screening raises questions for employers and insurers. Science. 1986; 232: 317-319.
9. Nelkin, Dorothy and Laurence Tancredi. Dangerous Diagnostics: The Social Power of Biological Information. New York: Basic Book, 1989.
10. Lappe, Marc A. Ethical concerns in occupational screening programs. Journal of Occupational Medicine. 1986; 28(10): 930-4.

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Air Ambulance: Utilization in Southern Ontario, Patient Characteritics, and Patient Transport Routes

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Abstract

This article is intended (i) to provide an overview of the Air Ambulance Program operating out of Sunnybrook Health Sciences Centre and, (ii) to summarize a retrospective study which characterized the Sunnybrook HSC trauma patients utilizing the air ambulance in south-central Ontario.

A review of hospital records for an eleven month period indicated that two distinct groups of patients are being airlifted; those who arrive directly to the hospital from the trauma scene and those who arrive from peripheral hospitals (i.e. different routes of transport). To assess the effectiveness of the current transport routes, survival probabilities (Ps) were calculated for a smaller subgroup of patients. It was found that low risk patients (high Ps) had survival rates approximating their predicted rates while low survival probability transfers (low Ps) exceeded the predicted survival rates. However, patient survival in the intermediate probability range (Ps between 50-75%) was the lowest of the predicted probabilities. This suggests that current triage protocols, which include route/mode of transport, may lack sensitivity to this population of trauma patient. It may also indicate that at a closer scrutiny of this patient group may be required to identify parameters which may need evaluation so that appropriately timed treatment may be instigated to improve survival.

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Background

The Need for Air Amublances

Trauma is a significant consumer of health care resources and has a considerable biopsychosocial and economic impact. Canada's spending on social services is estimated to be about 21% of the GDP and has been increasing at a rate of about 2.9%/annual[1]. Trauma is one of the major causes of lost economic potential as measured by disability days (15.7 days per year per person). In the United States, traumatic injury is one of the leading causes of lost economic potential as expressed by the Potential Years of Life Lost (PYLL). The cumulative mortality cost is approximately 200 billion dollars (in 1991 US dollars)[2]. The primary reason for this high value is that most trauma patients are young, hence, a great proportion of their productive life is lost. It is obvious that the inevitable incidence and cost of trauma must be managed in a way which balances outcomes of injury and costs of these outcomes. Cost control may be exerted very early in the treatment of these patients by effective and appropriate triage of trauma patients. Use of appropriate levels of care minimizes the cost, mortality and morbidity, which result from inappropriate management of traumatic injury[3].

Deaths due to trauma have been strongly correlated with deficiencies in emergency transport systems[4]. Often, patients waste time at local hospitals in need of definitive diagnosis and intervention, and occasionally succumb to their injury due to inappropriate triage or care[5]. To

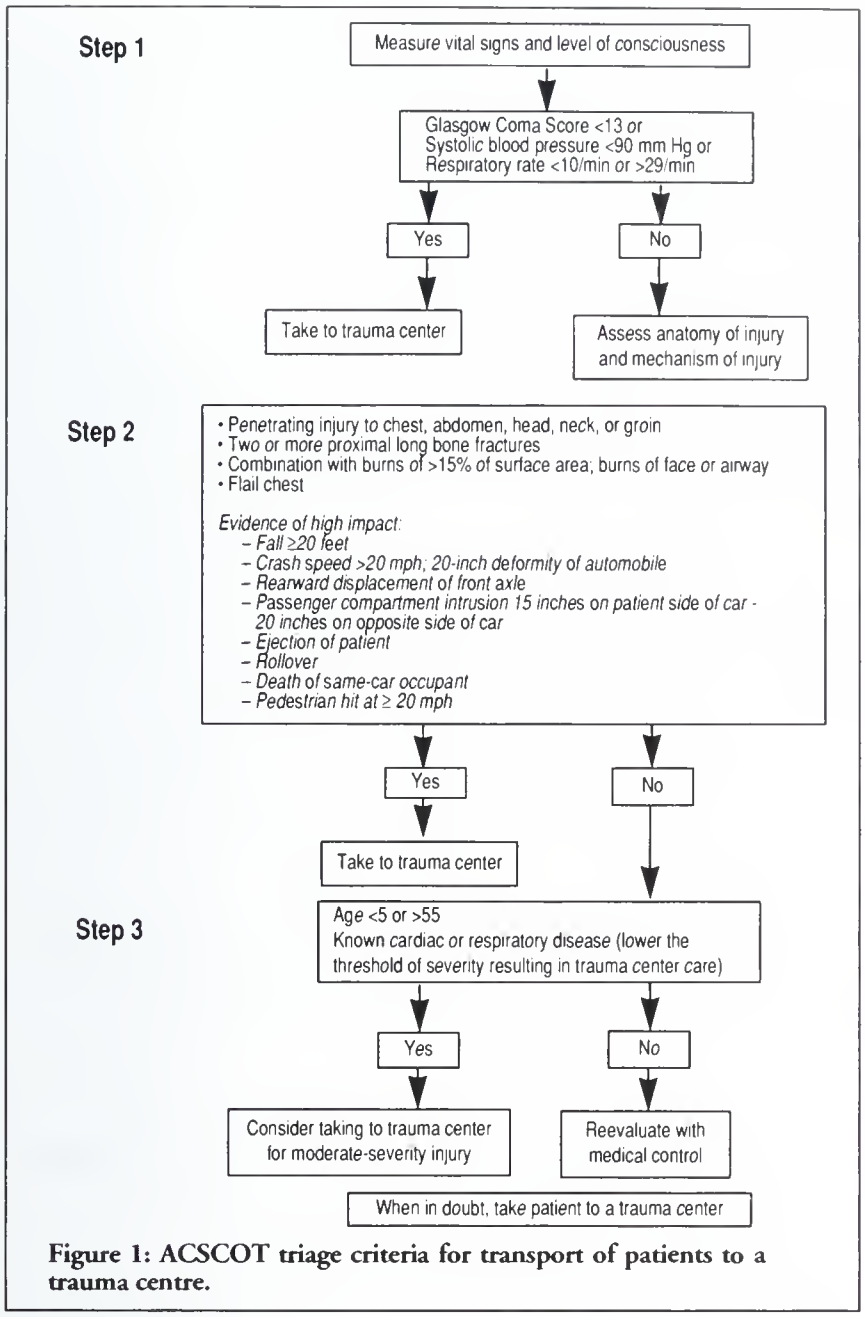

Step 1
Measure vital signs and level of consciousness
Glasgow Coma Score <13 or
Systolic blood pressure <90 mm Hg or
Respiratory rate <10/min or >29/min
Yes
No
Take to trauma center
Assess anatomy of injury and mechanism of injury
Step 2
• Penetrating injury to chest, abdomen, head, neck, or groin
• Two or more proximal long bone fractures
• Combination with burns of >15% of surface area; burns of face or airway
• Flail chest
Evidence of high impact:
– Fall ≥20 feet
– Crash speed >20 mph; 20-inch deformity of automobile
– Rearward displacement of front axle
– Passenger compartment intrusion 15 inches on patient side of car - 20 inches on opposite side of car
– Ejection of patient
– Rollover
– Death of same-car occupant
– Pedestrian hit at ≥ 20 mph
Yes
No
Take to trauma center
Step 3
Age <5 or >55
Known cardiac or respiratory disease (lower the threshold of severity resulting in trauma center care)
Yes
No
Consider taking to trauma center for moderate-severity injury
Reevaluate with medical control
When in doubt, take patient to a trauma center

Figure 1: ACSCOT triage criteria for transport of patients to a trauma centre.

address these problems, regional trauma centers and triage programs have been developed. Specific triage criteria for transport of patients to a trauma centre has been established by the *American College of Surgeons' Committee on Trauma (ACSCOT)* (Figure 1). Once triaged to the appropriate level of care (trauma centre or local hospital) the next step in the management process is transfer. Indications for activation air ambulance have been proposed[4,5,6,7,8] but not incorporated into the transport decision process or algorithm. The transport of severe trauma patients is best managed by air paramedics, operating with specific protocols, and providing aggressive care[6,9,10,11,12,13,14,15,16]. However, limited availability of air ambulance necessitates that land and air services operate cooperatively to ensure adequate coverage and service delivery. Careful planning and protocols for air ambulance use will reduce ineffective service provision.

Triage

When to Use Air Ambulance

Aeromedical flight teams have several potential advantages over conventional prehospital care: they provide a higher level of medical expertise and intervention at the scene and during transport; the transport to the hospital requires much less time; and they can transport severe trauma patients directly to a trauma centre even if it is not the closest facility[15,16]. It should be noted that all trauma patients do not need immediate transport to a trauma centre via air ambulance since over-triage may have a congestive effect on the emergency medical services (EMS) and constitutes a waste of health care system resources[7,17]. However, over-triage or overuse of trauma centers as high as 50% has been considered necessary by the American College of Surgeons in order to maintain an acceptable minimum level of under-triage in a community[18].

The limits of acceptable time and route of transport within the ACSCOT algorithm has been only modestly addressed. Delays in transferring patients to a trauma centre, due to diagnostic and treatment procedures at the primary receiving hospital, have been shown to increase mortality rates in patients with blunt injury if transport delays were more than 4 hours post-accident[18]. The patients which benefit most from this stopover are those who are more seriously injured (i.e. high Injury Severity Scores (ISS) values)[19,20]. The ISS is derived from assessments of injuries in specific areas of the body, called the Area Injury Score (AIS). The actual ISS value is the sum of squaring each of the three highest AIS values.

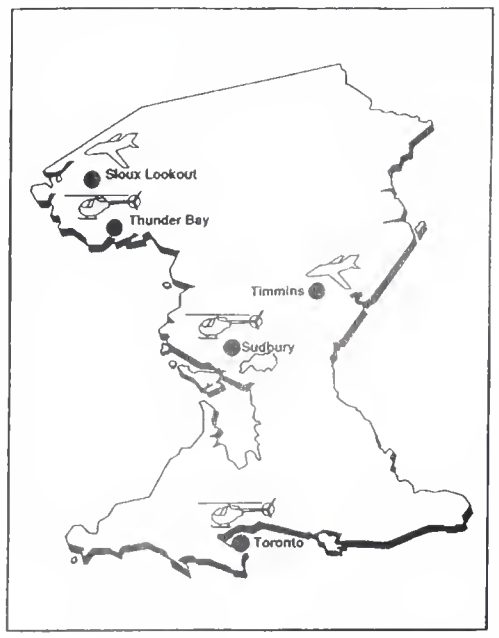
Patients with mid-severity injury (ISS of 25-40) need to be identified rapidly since this group of patients have been shown to be most sensitive to increased delays[8]. These patients have disproportionately increased needs for in-hospital and post-hospital rehabilitation[21] which increases the annual costs of their treatment 3 to 9 fold above the cost of treating the acute injury. This obviates the need to include patient transfer route in the overall triage algorithm.

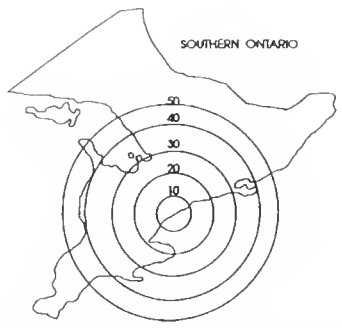
Air Ambulance Program and Sunnybrook Health Sciences Centre

The helicopter program in Southern Ontario has its training operations at Sunnybrook Health Science Centre and its operation base at the Toronto Island Airport. The Ontario Ministry of Health funds and directs the operations and is based in North York, Toronto[9,12,13].

Ontario's aeromedical transportation systems, funded by the Ontario Ministry of Health, is a large complex operation based on the concept of inter-regional coordination and management[22]. It spans the province (412,582 square miles) with a network of fixed wing and helicopter services both dedicated and chartered (undedicated) and serves a patient population of 15,000 annually[23]. The Toronto component covers a principal response radius extending from Kingston to London (east to west), and Perry Sound to the north, and a secondary response area, Ottawa to Windsor, and Sudbury/Northbay area (less than 55 minutes flight time one way (Figure 2). The patient contact frequency is about 750-1000 calls/annum and of that, about 15-20% are trauma patients. The remainder of patients are geriatric, pediatric, neonatal or medical patients requiring interhospital transfers. A significant proportion of Toronto air ambulance calls originate from the rural areas of the helicopter's response area[23].

Three major patient types of patient transports are serviced: (i) acute trauma victims transported directly from accident scenes and who require advanced life support by





Air Ambulance Helicopter Flight Times (Minutes from Toronto. Times include 5 minute warm-up period before takeoff.

Figure 2: Air Ambulance Bases

The ministry's Dedicated Air Ambulance Program operates out of one southern base at Toronto and four northern bases (Sioux Lookout, Timmins, Thunder Bay, and Sudbury).

paramedics ("direct transports"), (ii) patients whose initial trauma has been stabilized by a medical team at a hospital and require transport to a facility with expertise in specific procedures or diagnostic capabilities ("indirect transports"); and (iii) critical care patients requiring specialized facilities necessitating interhospital transfers.

The population base is quite underserviced by air ambulance according to various calculations[18]. Several multivariate studies[1,23,24] support the argument that helicopter transports provide an adequate return on investment in pre-hospital care expenditures, in both cost-effective transport of patients, and in better patient outcomes as seen by reduced morbidity and mortality, and hospital costs.

The air ambulance crew are trained as Emergency Medical Care Assistants (EMCA) and have specialized training in aeromedical procedures. The crew are authorized to perform delegated medical acts on a standing order basis. They also carry out specific procedures under the direction of the caring physician via direct communication.

The decisions to mobilize the regional helicopters (i.e. the Toronto Island based Sikorsy S-76, "Bandage I") is determined by the land-based crews arriving at the scene or by attending physicians in local facilities to which the patients are first brought.

Helicopter mobilization criteria for transferring trauma patients to the regional trauma centers have been established for some time (ACSCOT). Studies comparing differences between patient transfers directly to trauma centers, or indirectly, via a stopover at a local facility, have not been conducted. It was recognized that having delineated criteria for choosing specific transport routes may improve patient outcomes. Currently, the aeromedical crew, with physician consultation, decides when direct transport is warranted once they arrive at the scene. No definitive criteria had been instituted at the time the study was initiated. However, the trauma teams at Sunnybrook HSC identified situations in which aeromedical crews should bring patients to a local medical facility prior to SHSC. Essentially, local hospital stopovers should be made if the air paramedics are unable to treat the injury sufficiently (i.e. limited intervention options, or time limits):

a) if the transport is going to be too long and class III or IV shock is present requiring large volumes of blood to be transfused.

b) if there is significant chest (penetrating or blunt) injury requiring chest tube or surgery and the patient is more than 30 minutes from level trauma I centre.

c) tenuous airway - intubation is difficult or impossible (i.e. facial smashes).

Trauma Patients Utilizing Air Ambulances Services to Sunnybrook HSC

Data on the utilization of the air ambulance services by all patient types has been evaluated in the past as part of a quality control plan[25]. However, characterizing trauma patients and their outcomes has not been conducted. This type of information is valuable for the air paramedic training and for program directors considering routes and modes of transport for trauma patients.

Methods

The specific population to be studied is the group of trauma patients transferred to Sunnybrook HSC by the air ambulance in 1992. The 1992 population was chosen to

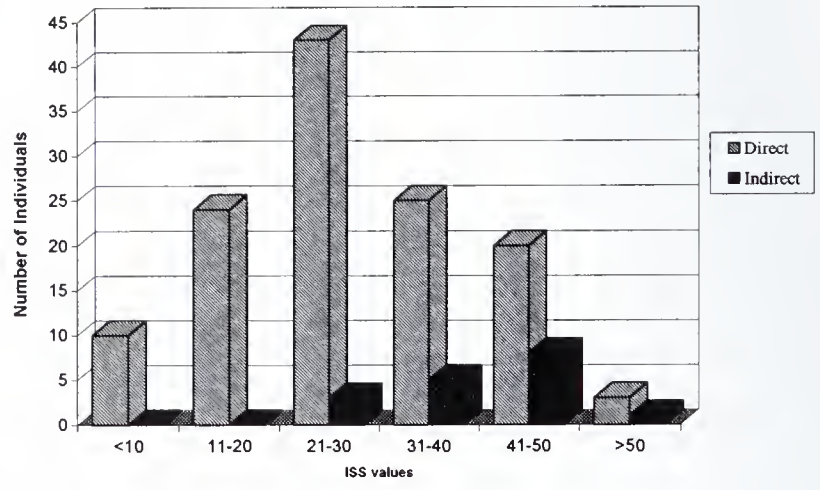


Figure 3: Direct vs Indirect Transport of Patients by ISS

Table 1: Profile of Patients Utilizing SHSC Air Ambulance and Trauma Centre Facility

Characteristic	Survivors	Non-survivors
Age	35	41
ISS	25.68	40.88
GCS	11.08	7.63
% pt. with GCS < 4	17 %	94.12 %
No. systems involved	3.64	3.53
Incident Type		
MVA	75.92 %	41.18 %
Fall	4.63 %	23.53 %
Motorcycle	4.63 %	11.76 %
Bike	0.93 %	5.83 %
Pedestrian	6.48 %	5.83 %
Other	7.41 %	11.76 %
Type of Admission:		
Direct transport	25.9%	29.4%
Referred transport	74.1%	70.6%
Referring centre GCS:		
Direct transport	12.96	3.00
Referred transport	10.82	7.57
Average time to SHSC	258 min.	180.6 min

Table 2: Injury Characteristics

Characteristic	Survivors	Non-survivors
Most severe AIS		
Head/Neck	54.20 %	64.71 %
Chest	23.36 %	29.42 %
Abdomen	9.35 %	5.88 %
Limbs	12.15 %	0.00 %
Other (face/multiple)	0.93 %	0.00 %
System Scores (AIS)		
Head/neck	2.82	4.18
Chest	1.84	2.76
Abdomen	1.00	1.24
Limbs	1.86	1.82
Face	0.56	0.18
Extremeties	1.06	1.29

ensure that the complete hospital stay history was available and that intervention and outcome information (procedures, length of stay (LOS), discharge types) was available.

A retrospective study was conducted to characterize the population (n=126) of trauma patients. Parameters reviewed were annual use pattern, population demographics, and various characteristics based on two sub-groups: the survivor group (SG) (n=109) and the non-survivor group (NSG) (n=17). The transport routes utilized by these two groups was also reviewed. The sources of the information were the *SHSC-Trauma Patient Record of Stay* forms and flight information sheets.

Unfortunately the study population was a small group of patients and as such, did not permit statistical analysis to verify significance of the parameters studied once it was dissected into smaller groupings. Hence, trends and correlations are primarily based on normative comparison (i.e. percentages). To increase confidence in the results, a much larger population must be obtained by pooling the data of several years of transfers. This may prove difficult because information on the patient transfer forms gathered prior to 1992 is sparse and detailed analysis may prove to be difficult.

Table 3: Intervention Performed

Characteristic	Survivors	Non-survivors
Chest tube (no./patient)	0.39	1.00
Pt. with chest tube	29.63 %	35.29 %
• referred	18.52 %	100.00 %
• direct	11.11 %	0.00 %
Crystalloids administered		
>3000 mL	21.30 %	47.06 %
>2000 mL	36.11 %	76.47 %
0 mL	16.67 %	5.88 %
Fluid Resusitation		
Total Volume (Ave.)	1811.57 mL	3651.67 mL
Packed RBC	0.64 units	2.40 units
Plasma	0.06 units	0.13 units

Results and Analysis

Temporal Consideration

The SHSC trauma centre receives several hundred trauma patients annually. The involvement of the air ambulance in patient deliveries has been steadily growing since 1989 and constitutes about 20-25% of trauma patients received at Sunnybrook HSC. The highest number of air ambulance trauma transfers occurs in summer months (August) and early fall (October). This seasonal variation in frequency of air transports has been described in other regions[14,21] and is correlated with increases in trauma room activity (peak between May to October) which reflects increases in travel and recreational activities during this period.

Surviving and Non-surviving Patient Parameters

The survivors are younger (Table 1), have lower ISS values, higher Glasgow Coma Scores (GCS), and fewer anatomical systems involved. Substantially fewer survivors have GCS<4 (severe neurologic effects). The combination of age and injury severity has been shown to be effective prognostic indicators[27]. A measure of sensitivity of patients to their injury is the LD_{50}. The LD_{50} is defined as lethal dose causing 50% mortality in a population exposed to an event. The "event" in his case is the injury severity and/or type. It has has been described that the LD_{50} decreases with age[28]. This means that at any severity

of injury, older patients will have worse prognosis. The data found in the trauma patient population at SHSC was found to be in agreement with this previous finding. Differences in the incident type were also apparent. Non-survivors had a greater proportion of falls and motorcycle accidents. Hence the cause of the injury may also be considered in the prognosis and also perhaps in the urgency of transport. This, however, would require futher investigation to validate.

It was found that in both SG and NSG, head/neck and chest injuries were the principal sites of injury (Table 2). The AIS values (AIS ranges from 0-5 on a standard evaluation scale) for both of these regions were considerably greater in the non-survivors. Many of the severe head injury patient deaths occurred within the first 24 hours and many occur at the scene. This shows that head trauma is a significant factor in patient outcome and that in combination with chest injury, the prognosis is poor.

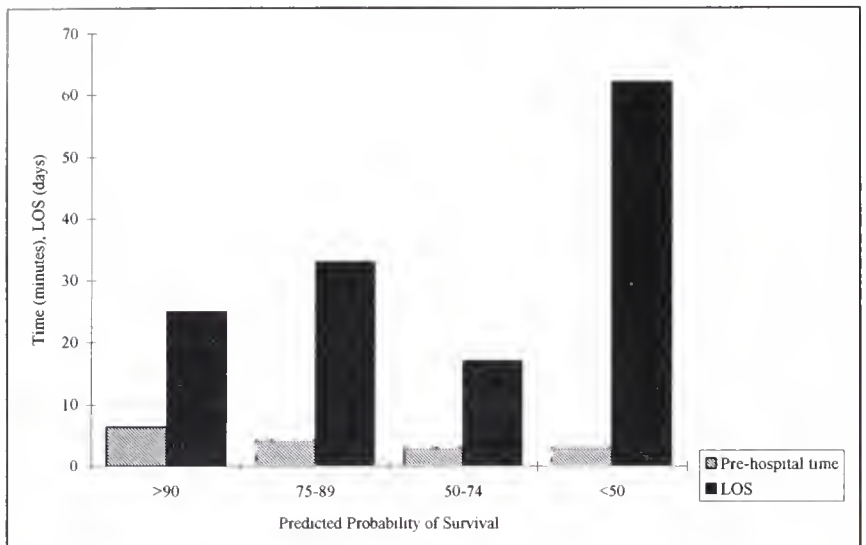


Figure 4: Survival Probability as Related to Delays and LOS

Note: Lower Ps = increased LOS implying severe injury. Shorter pre-hospital times are found with low Probability of survival (Ps).

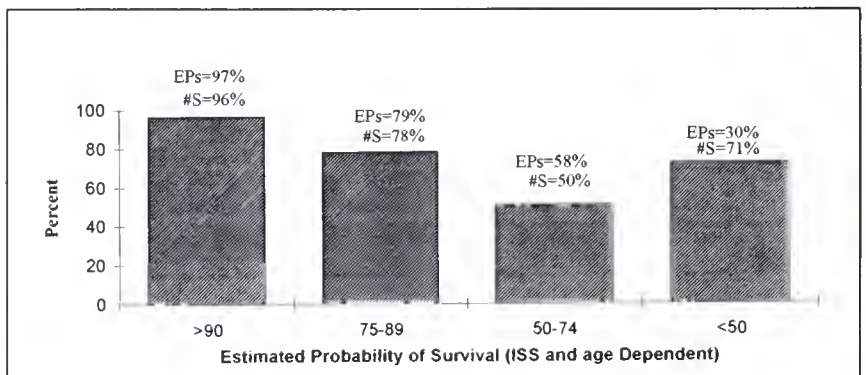


Figure 5: Predicted versus Actual Survivors

EPs = Estimated Probability of Survival; #S = Number of Survivors at the designated quantel.

Difference in the GCS of the SG and NSG are described in Table 3. The SG transported directly from the scene had higher GCS than indirect transfers. This may indicate that the referring physician failed to identify all of the injuries immediately or the patient's condition had deteriorated to a point which was beyond the capability of the facility to handle. The NSG had lower GCS in the direct transfers indicating that appropriate triage is carried out in the field, at least for the more severe cases[29]. In both transport types, however, the non-survivors had lower scores indicating a possible need for earlier intervention by a regional trauma centre.

For both transport types the ratio of SG:NSG is about the same (6:1) and within each survivor category, the ratio of indirect:direct transport is 3:1(Table 3). At all ISS intervals, most of the patients are being transported from the scene to local hospital and then to SHSC (Figure 3). Concomitantly, at higher ISS values the proportion of patients being transported to a trauma centre directly was found to be increasing. This suggests that the empirical route selection protocol being utilized is effective.

Both patient groups were given aggressive fluid and ventilation resuscitation (Table 4) which has been strongly correlated with improved survival[12]. None of the NSGs were breathing spontaneously upon arrival. However, the survivors showed a 46% increase in the number of spontaneous breathers upon getting to SHSC. This reflects the resuscitation efficacy in the SG by (i) the local hospital and, (ii) the aeroparamedic monitoring and stabilizing during transport. The NSG received nearly two fold more fluid resuscitation than the SG indicating their instability.

Patient Outcome analysis

Death due to trauma follows a trimodal distribution. Many patients die at the scene of the trauma from severe injury before dispatch of the helicopter. Secondary deaths are found to complete the injury sequelae within 24 hours (approximately 50% of deaths at SHSC) and the third phase occurs beyond 44 days (2 deaths). Therefore, the average patient transferred by air ambulance to Sunnybrook HSC, who survives the first day, will have a greater than 98.4% of leaving the hospital alive. This demonstrates the effectiveness of the trauma management process.

The average length of stay (LOS) in Ontario hospitals is about 11.4 days while Canadian average was 11.8 days[1]. In comparison, a great proportion of the SHSC patients (60%) are taking longer than the national and provincial averages to leave the hospital.

In both transport routes, similar proportions of patients had LOS of less than 14 days (direct transfers 38%; indirect transfers 41%). However, when corrected for deaths (LOS < 1), the survivors of the direct transports (n=6) with LOS of 1-14 days constitutes about 19% of the route-specific survivors. The indirectly transferred patients with LOS of 1-14 days consist of about 29% (n=27) of the surviving route-specific survivors. This is significant in two ways. Firstly, it demonstrates that a greater proportion of patients transported indirectly leave the hospital with in the average expected time. Secondly, it underscores the difference between the "average patient" in the general hospital populations and the trauma patients being brought to the trauma center at Sunnybrook HSC. Specifically, the SHSC patients suffer

from considerably more significant medical complications. Further, this difference may be due to variation in type and extent of injury, and/or the type and timing of intervention by medical personnel. This provides further support for the argument that hospitals in proximity to accident scenes should be used regularly for patient stabilizing procedures.

Survival Probabilities (Ps) and Outcomes

Probabilities of survival (Ps) can be estimated based on ISS and age along with several variables[27]. Recall that these were the two most significant factors related to the LD50 of a sustained injury[28]. A limited group of patients (n=46) was used for survival analysis due to the limits of the table of values available (survival probability of 3-97%; ISS 25-50, age 35-65). It is assumed that beyond these values, the variables are not as effective in prediction.

As the probability of survival increases, the length of stay was found to decrease (Figure 4). This was assumed to verify that the LOS was dependent on the extent of injury. The pre-hospital delay was found to decrease as the probability of survival decreased indicating that the severely injured patients are being transferred earlier to the regional trauma centre at Sunnybrook HSC. Patients generally had lower GCS, higher ISS values, and increasing lengths of stay as their probability of surviving decreased.

When the predicted and actual outcomes are compared (Figure 5), the Ps<50 group is found to benefit most from this mix of decreased transit time, increased intervention. This was supported by the fact that the actual number of survivors was more than 2 times that of the average expected values. The higher Ps groups had actual survival rates closely approximating the predicted values. This suggests that they are being treated appropriately. The group of patients with Ps range 50-74 was notably different from the others. Their average estimated Ps was on the low end of the range (average Ps of 58%) and their outcome was also low (50% survivors). This group must be the target of intense analysis to determine parameters which need to be managed more aggressively in all three phases of care (pre-hospital care, hospital treatment, and rehabilitation).

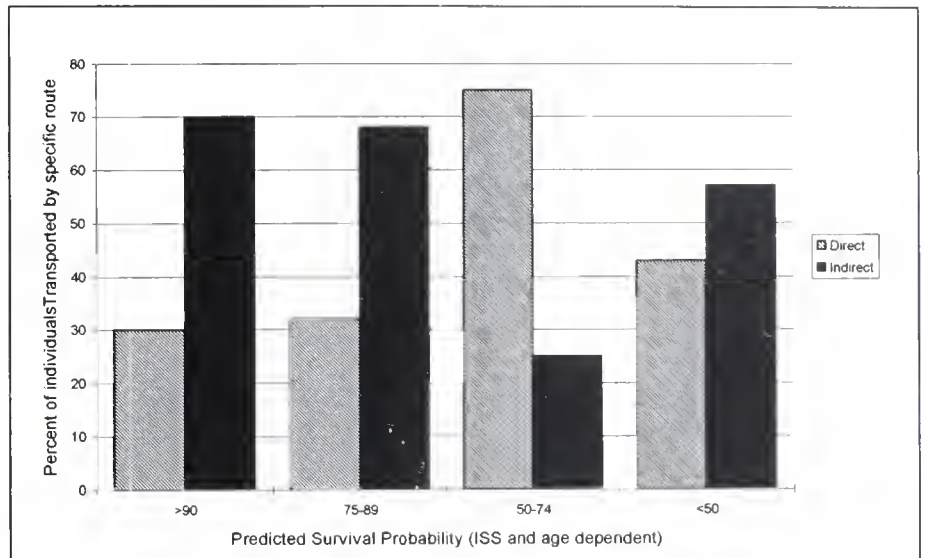


Figure 6: Percent of Patients at Various Survival Probabilities as a Function of Different Routes

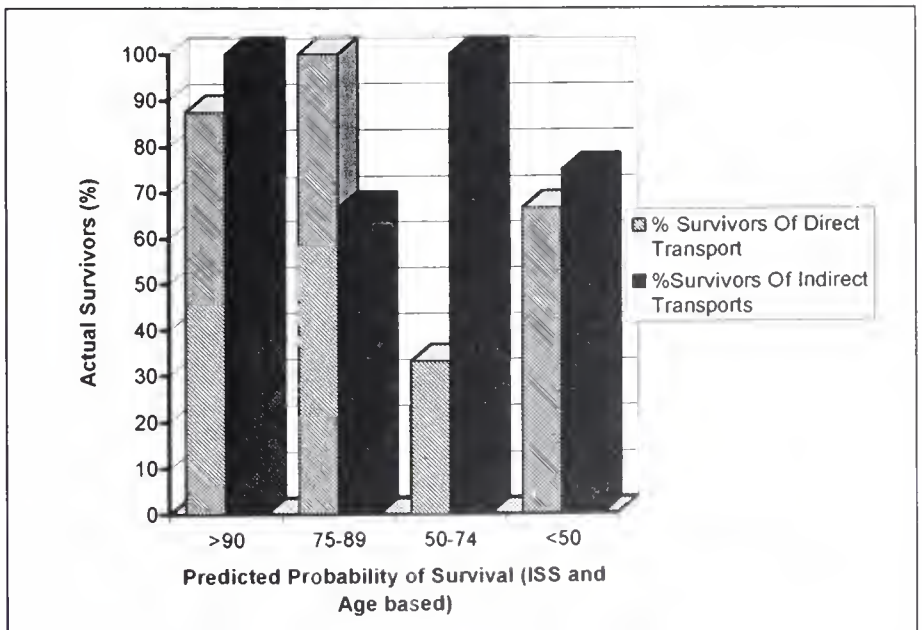


Figure 7: Effects of Transport Route on Patient Survival

To address this issue partially, the transport mode was reviewed for these patients. Surviving patients within the Ps>75% and Ps<50% groups were predominantly transferred from referring hospitals (Figure 6). In the group with Ps 50-74% direct transports were most frequent. When the actual survivors of each transport mode are assessed, the Ps 50-74% group did have greatly reduced number of survivors in the direct transport mode (Figure 7). In fact, only about 33% of the direct transport patients survived their hospital stay in this Ps group. This implies that this group may be better managed if local intervention was instituted early. It should be pointed out that this group needs to be evaluated more closely to determine differences in the patients transported by different routes.

The Ps<50% group had essentially the same survival outcomes independent of transport route with only a marginal benefit in the indirect transport group. This indicates that the route of transport with Ps<50% has little effect on the expected outcome, i.e., patients who are assessed at the scene as having a Ps<50 (based on a formula of age and ISS as described by McLellan et al[27]) are perhaps better served by being transferred locally for initial treatment provided that the land trip is shorter than the expected round trip for air ambulance. Interestingly, the Ps 75-89 group had preferential outcomes in the direct transfers. This is supported by other studies[5,8].

Conclusions

The air ambulance service is a cost effective measure in the overall treatment process of traumatized patients. However, due to the time commitment required for air transport and the sub-optimal availability of the helicopter, it is essential to identify specific variables which may be considered prior to transport of patients by this method. A review of a small portion of the Sunnybrook

HSC trauma patients revealed specific characteristics of successful (surviving) and unsuccessful transports.

In general, older patients, with higher ISS values, with lower GCS, with multisystem injuries, requiring significant resuscitation efforts tend to do poorly. Trauma patients with significant head and neck injuries concurrently with chest injuries do poorly independent of transport mode suggesting that closer evaluation this group needs to be conducted to determine the attributes of a salvageable trauma.

Patients with calculated theoretical survival probabilities Ps>90% do not appear to benefit from air ambulance transport. More specifically, they did not benefit from direct transport to the trauma centre. This suggests that they may be adequately served in a facility other than a regional trauma centre. Also, patients in the Ps 50-74% group were found to be in need of better management as evidenced by the actual survivals being less than expected. These findings were consistent with previously published results[8]. Therefore, further study of this group must be carried out to identify variables which may be used on the scene to estimate their survival probability.

At this point, it is still not obvious whether patients should be triaged directly from the scene to SHSC or indirectly via a local hospital for intervention. The use of a helicopter for patient transport to local facilities instead of land ambulance is expensive and not an effective use of resources. This means that land crews who arrive on the scene must use more stringent criteria to decide whether the helicopter should be called. This is expected to be a fine tuning of the already established protocols for transport (ACSCOT) and lead to decreased costs of providing the air ambulance service. Concomitantly, better access of trauma patients to appropriate level of services (local hospital or regional trauma centre) at the appropriate time is expected to decrease morbidity costs (economic effects of lost productivity and capital costs), as well as, suffering by the patients.

Acknowledgments

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References

1. Sutherland RW and Fulton MJ. Health Care in Canada: A description and analysis of Canadian Health Services. 1988, The Health Group, Ottawa, Canada.
2. Runge JW The cost of injury. Emerg Med Clin North Am 1993; 11(1): 241-253.
3. Blackwell TH Prehospital care. Emerg Med Clin North Am 1993; 9(1): 1-14.
4. Urdaneta LF, Sandberg JK, Cram AE, et al1. Evaluation of an Emergency Air Transport Service as a Component of A Rural EMS System. American Surgeon 1984; 50(April): 183-188.
5. Champian HR, Sacco WJ, Carnazzo AJ, Copes W, and Fouty WJ. Trauma Score: Critical Care Medicine 1981; 9(9): 672-676.
6. Smith JS, Smith BJ, Pletcher SE, Swope GE, and Kunst D. When is Air Medical Service Faster than Ground Transportation? Air Medical Journal 1993; August: 258-261.
7. MacKenzie EJ, Morris JA.Jr, Smith GS, and Fahey M. Acute hospital costs of Trauma in the United States: Implications for Regionalized Systems of Care. J Trauma 1990; 30(9): 1096-1101.
8. Kearney PA, Terry L, and Burney RE. Outcome of Patients with Blunt Trauma Transferred After Diagnostic or Treatment Procedures or Four-Hour Delay. Ann Emerg Med 1991; 20(8): 882-886.
9. Hamman BL, Cue JI, Miller FB, O'Brien DA, House T, Polk HC, and Richardson DJ. Helicopter transport of Trauma Victims: Does a Physician Make a Difference? J Trauma 1991; 31(4): 490-494.
10. Burney RE, Passini L, Hubert D, and Maio R. Comparison of Aeromedical Crew Performance by Patient severity and Outcomes. Ann Emerg Med 1991; 21(4): 375-379.
11. Burney RE, Fischer RP. Ground versus air transport of trauma victims: Medical and logistical considerations. Ann Emerg Med 1989; 15: 1491-1496.
12. Schmidt U, Frame, SB, Nerlich, ML et al. On-scene Helicopter Transport of Patients with multiple injuries: Comparison of a German and an American system. J Trauma 1992; 33(4): 548-555.
13. Campbell JP, Low RB, and Bowman D. The Efficacy of Ground versus Helicopter Transport in Patient Outcome. J Okla State Med Assoc 1989; 82 (July): 311-314.
14. Jones SE and Brenneis AT. Study design in prehospital Trauma Advanced Life Support-Basic Life Support Research: A Critical Review. Ann Emerg Med 1991; 20(8): 857-860.
15. Fischer FP, Flynn TC, Miller PW, and Duke JH. Urban Helicopter Response to the Scene of Injury. J Trauma 1984; 24(11): 946-951.
16 Wright SW, Dronen SC, Combs TJ, and Storer DS. Aeromedical transport of patients with post-traumatic cardiac arrest. Ann Emerg Med 1989; 18(7): 721-726.
17. Cayton CG, Murphy JG, and Stahl WM. Basic life support versus advanced life support for injured patients with an injury severity score of 10 or more. J Trauma 1993; 35(3): 460-466.
18. Farnell MB and Sachs JL. (1989) Mayo Clinic's Hospital-Based Emergency Air Medical Transport Service. Mayo Clin Proc 1989; 64: 1213-1225.
19. Baxt WG and Moody P. The impact of Advanced Prehospital Emergency Care on the Mortality of Severely Brain Injured Patients. J Trauma 1987; 27: 365-369.
20. Baxt WG, Cleveland HC, Fischer RP et al. Hospital based rotor craft aeromedical emergency care services and trauma mortality: A Multicentre study. Ann Emerg Med 1985; 14: 859-864.
21. Siegel JH, Gens DR, Manantov T, Geisler FH, Goodarzi S, and MacKenzie EJ. Effective of Associated Injuries and Blood Volume Replacement on Death, Rehabilitation needs, and disability in Blunt Traumatic Brain injury. Crit Care Med 1991; 19(10): 1252-1265.
22. Wallace G Medevac. Ontario patient transfers spawn business and controversy. Aviat and Aerosp 1993; 66: 10-12.
23. Studnzia AB and Lumsden CJ. A Computer-Based Simulator for Air Ambulance System Analysis, Design and Optimization. Air Med J 1994; March: 96-103.
24. Bruhn JD, Williams KA, Aghababian R. True Costs of Air Medical vs. Ground Ambulance Systems. Air Med J 1993; August: 262-268.
25. McLellan B and Dempster A. Quality assurance in the inter-hospital transfer of trauma patients. Report presented at the Annual Meeting of the Trauma Association of Canada, September 1993; Vancouver, British Columbia.
26. Sellwood N. An ambulance helicopter for emergency calls. Arch Emerg Med 1992; 9: 280-289.
27. McLellan BA, Koch JP, Wortzman D, Rodgers C, Szalai J, Williams D. Early identification of high-risk patients using the "Estimated" injury Severity Score and age. Acc Annal Prev 1989; 21(8): 283-290.
28. Bull JP The injury severity score of road traffic casualties in relation to mortality, time of death, hospital treatment time and disability. Acc Anal Prev 1975; 7: 249-255.
29. Rhodes M, Perline R, Aronson J et al. Field triage for on-scene helicopter transport. J Trauma 1986; 26: 963-969.

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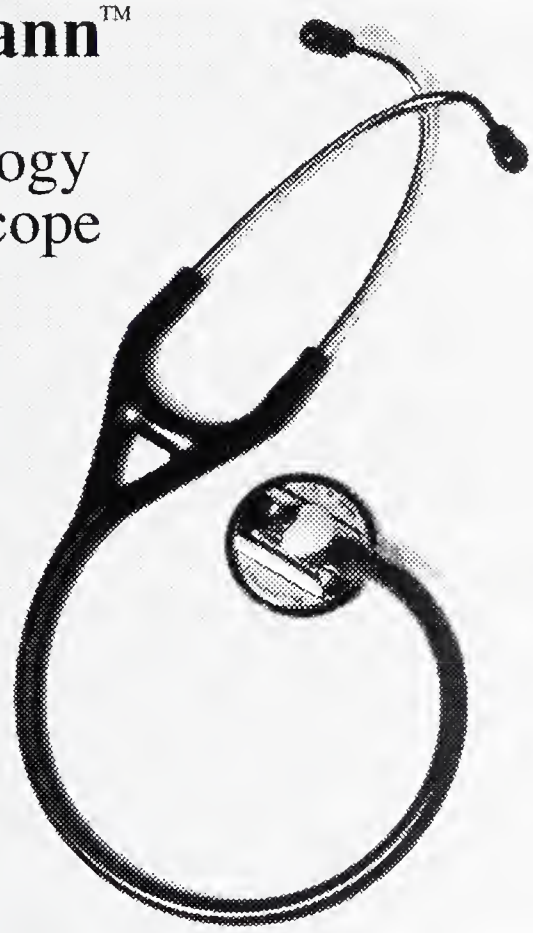

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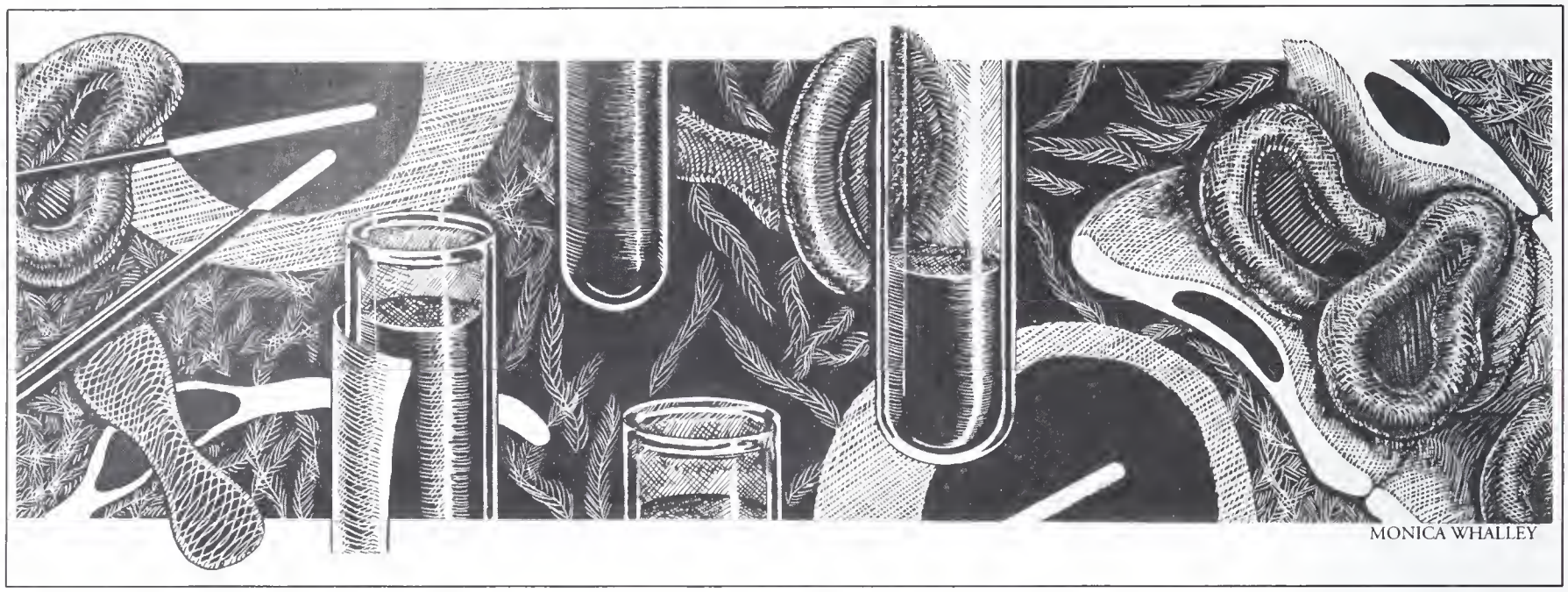
Quirt's Quarks

Ian C. Quirt, MD, FRCPC



B-Cell

The white count is high and the nodes are big
But the patient seems quite well
Lymphocytes abound in the blood
Then think about CLL

If no complications can be found
And the cells are all Bs not Ts
With mere observation or gentle meds
They will survive a long time with ease

The bones look like swiss cheese, the calciums up
And the kidneys don't work too well
The lab reports rouleaux and a high ESR
Myeloma should ring a bell

If you don't diagnose it at this point
The poor patient will likely decline
But with fluids, meds and radiation to bone
The person may feel just fine

If you find a macroglobulin
And you don't want the patient to die
Check the heart, lungs, eyes and skin
The viscosity may be sky high

You need not be brilliant to manage this
You don't need a Ph.D thesis
If you discover that the viscositys up
Perform a plasmapheresis

Chronic Myeloproliferative Disorders

If the red count is high, the spleen tip is felt
And there is normal O_2 delivery
The person itches like mad after a bath
Then think about PRV

The white count is high, the LAPs low
The Ph1 chomosomes found
There are increased polys with just a few blasts
A diagnosis of CMLs sound

If tear drop cells are found in the blood
And the spleen fills the tummys left side
Myelofibrosis will be seen
In the biopsy that you provide

If the platelets are high and theres no other cause
Such as occult bleeding or cancer
The patient does well with just aspirin or less
Essential thrombocythemias the answer

Coagulation

To tell if factor seven is low
A long PT is a useful sign
The PTT evaluates
Twelve, eleven, eight and nine

If a septic patient is bleeding
And you suspect DIC
Look for a low fibrinogen
And increased FDP

If the problem is mainly bruising
And the bleeding is petit not grand
Then think of the entity
Named for von Willebrand

If a patient is on heparin
For a clot from groin to knee
To give the ideal dosage
Request the PTT

To follow folks on coumadin
In labs both near and far
Discard the old prothrombin time
And use the INR

Blood Component Therapy

If the patient is quite anemic
And in a weak and feeble voice
Tells you he needs transfusion
Packed cells should be your choice

Pooled platelets should be ordered
But if they don't last for one day
You may need to switch to
Platelets matched for HLA

If a transplantS in the future
The best approach would be
Blood thats been irradiated
And is free from CMV

If the transfusion causes fever
And the reaction is repeated
Then give component treatment
That is leukocyte depleted

Transfusion is life saving
But there are dangers you must know
Transfuse sparingly and wisely
And the odds of problems will be low

Report from Egypt : Mummies, Medicine, and Daredevil Drivers

Dalia Eino, 9T7

Local Hospital in Rasheed

I arrived at the Cairo airport at 11 pm, exhausted from my 20 hour trip and anxious of what awaited me. Moments after entering the airport I spotted my supervisor, Dr. Siham Abdul Rihman, who although a total stranger, was easily identified by the sign she carried ...'Dr. Dalia - Welcome'. Now the fear really set in. In my jet-lagged state I had trouble recalling how I had named myself in the last letter but I was SURE it was not 'Doctor Dalia'. How could I explain, in my broken Arabic, that although I was almost a doctor (give or take a couple years) my abilities really did not extend far beyond the palpation of a spleen and the DDx of right shoulder pain. I decided that for the time being what she didn't know would not hurt her.

After clearing customs and finding our waiting car the adventure really began. While the drive to Cairo was a mere 30 km from the airport - it seemed never ending. The daredevil style of the driver - weaving in and out of traffic, blaring his horn at everything in sight - soon had me hiding underneath the dashboard. Even at this late hour the streets were overflowing with taxis, buses, donkey-drawn carts and people. It took everything in me not to pull out my eye chart to determine the visual acuity of the driver - suddenly it seemed like all moving objects were road targets and the lights and lane dividers were mere street decorations. Miraculously, we arrived safely at the dorm and I was never so thankful to get out of a car.

And while I thought that the drive was a learning experience, it paled in comparison to the many lessons that I learned during the next three months in Egypt.

The majority of my work was done at Abu Rish Paediatric Hospital in Cairo. This government institution was built ten years ago by Egyptian and Japanese architects and was referred to by the local doctors as 'state of the art'. Since the earthquake three years ago, which knocked down Cairo's General Paediatric Government Hospital, Abu Rish is now the only hospital of this nature serving Cairo and the surrounding Delta area. The case load at the hospital has been overwhelming due to the enormity of the population which it serves. There was never an empty bed among the 700 beds of the hospital. This overload was quite evident by the number of children and parents waiting daily on the steps of the hospital, hoping that 'today' would be the day they are told that one of the beds had become available for their child.

Along with the in-patient wards, Abu Rish is equipped with an out-patient clinic, where I spent most of my mornings. My first day at the out-patient clinic I was shocked at the number of people in the hallway waiting to see the doctor. I soon learned that no appointments are made, as medical attention is on a first come first serve basis and an hour's wait is nothing!

On a typical clinic day, two or three doctors plus myself would see 120-160 patients. Needless to say, a complete history or physical examination was rarely accomplished. Nevertheless, the doctors amazed me with the amount of

information they were able to obtain in a very short period of time. This efficiency was no small feat, seeing as most of the patients (or patient's parents) didn't answer the questions directly the first time around. And to this day I still can't figure out why so many parents felt that their neighbours' affairs were an integral part of their child's medical history.

The out-patient clinic was equipped with the bare necessities - an examination table, a desk and chair, a broken scale for babies and one for older children. Locked up was a blood pressure cuff, a flashlight and a stethoscope. We brought along tongue depressors, an otoscope and most importantly, lollipops.

The clinic provided services to all residents of the area, regardless of social class or religious affiliation. A check-up at this government hospital only cost 50 piasters (20 cent Cdn) and most medications could be obtained at the hospital pharmacy free of charge.

Most of the presenting complaints at the clinic were of a general nature such as diarrhea, dehydration, malnutrition, respiratory tract infections, chicken pox, scabies or bacterial infections. Most of the diseases stemmed from poverty, lack of health education and lack of proper sanitary facilities. Being a government hospital and basically free of charge, the majority of patients were from a low socioeconomic class.

Children's Outpatient Clinic

In the evening I did rounds on the in-patient wards. These were no better equipped than the out-patient clinic. The medical supplies cabinets were often bare, the equipment looked like it had been there since the opening of the hospital, and regardless of what it was you were looking for, there always seemed to be a shortage. This meant that doctors had to rely heavily on past experience, instinct, and excellent clinical skills to diagnose and treat patients.

As I walked down the halls of this 'state of the art' hospital I couldn't help but take note of the empty diagnostic labs, the make-shift incubators and the walls which desperately needed a paint job. In a country of 60 million people there are not enough health care dollars for government hospitals to be properly equipped, staffed or maintained. This is in striking contrast to the private hospitals, several of which I had the chance to visit. In these hospitals, care, medication and surgical supplies are paid for by the patients. Consequently the equipment is up-to-date, the staff is better qualified and health care is superior both in quality and quantity.

At the Abu Rish government hospital, the patients are not required to pay fees for their stay or for any medication which they received from the hospital pharmacy - which was often very low in supplies. However, items such a syringes, cannulas for I.V.s, and drugs not stocked in the hospital pharmacy had to be paid for by the patient's family. For most, the L3($1.00 Cdn) for a syringe or L6($2.00 Cdn) for antibiotics, although expensive, was attainable. Unfortunately, for one too many the L6 stood in the way of their child's treatment. In these situations, doctors often had a small stockpile of such supplies, obtained via donations, which they would distribute as needed. And when that supply was inadequate, it was not uncommon to find the doctors digging into their pockets and giving the patients the money needed to pay for the required supplies. The gratitude seen on the parents faces is something I know I will always remember.

On the wards I couldn't help but notice the distinct difference in the noise level between our quiet, organized Hospital for Sick Children and this paediatric hospital. Being right in the heart of Cairo, a city of 16 million people and nearly as many cars, Abu Rish is surrounded by the sounds of blaring horns, passing metro cars, the calls of street vendors and the voices of people - lots of people. Once inside the hospital the sound of children laughing, playing, yelling and crying echoed through the hallways. Added to this were the voices of parents arguing with nurses and doctors, demanding more attention for their children, requesting more medication or just venting their fears and frustration. Everyone seemed overworked, exhausted and irritated by the intolerable heat (27°C is considered a 'cool''summer's day). The only peaceful sights were those of mother's cradling their children and praying for their quick recovery.

A foreigner walking onto a ward at Abu Rish would be shocked by the number of people in the rooms. Although the wards only had a maximum of 12 beds per room, one could easily find 30-40 people in the rooms at any given time. This was largely due to the continuous flow of visitors. Aside from the mothers, who are admitted into the hospitals with their children, families

come to visit daily; not only fathers and siblings, but aunts, uncles, cousins, grandparents and friends as well. Although most visitors lived in nearby villages or the outskirts of the city, it became apparent how remarkable the daily voyage was when I discovered how much time, effort, money and planning such trips took. Nevertheless, the visits were made religiously and the visitors always brought treats for the child and mother.

The range of medical pathology seen was incredible and the stories accompanying them were even more so. A medical history could easily take an evening. The patients and their stories added a whole new dimension to medicine. On the whole, most cases admitted to our ward - a general paediatric ward - were related to dehydration usually secondary to diarrhea, severe malnutrition, accidents endured while playing, and parasitic infections. One of the tragic cases which I saw was that of a 6 month old baby girl. She looked extremely wasted, dehydrated and deathly ill on admission. Her mother told us that the girl had had severe diarrhea for two weeks. A week after the onset of the baby's diarrhea the mother took her daughter to see the village doctor at the local Health Unit. She reported that the doctor had told her to refrain from feeding the child and to administer an oral hydration solution (which she brought along with her - the package was not yet opened). I was alarmed at the medical neglect and the state of the baby. When pressed as to how long the doctor had told her to refrain from feeding the baby, she said she couldn't quite remember - she only remembered the order of cessation of food. As for what she had been doing for the last week, she informed us that she decided to refrain from giving the child anything, including the rehydration solution, in hope of stopping the diarrhea, which she told us was due to too much fluids! The girl was immediately admitted to the intensive care unit and rehydration commenced. Unfortunately, the shock was too much for her little body and she died the following day.

Admittedly, at first I was struck by the apparent poverty of the patients, however after working with them I realized that they had a wealth which money could not buy. The amount of love, support, faith and peacefulness that these people possessed was incredible. It never ceased to amaze me how warm, spirited and generous the patients and their families were. On one occasion when I had been away for five days doing field work, I returned to the warmest welcome from the patients, parents, doctors, nurses, caretakers and security personnel. One patient ran down to the canteen to buy me a Cola using her allowance, a mother made me tea (the national drink), and yet another offered me some of the food she had brought with her from the village for her and her son. Suddenly, I no longer felt like the "Canadian Doctor" but rather like part of their family - a family which encompassed the entire ward and staff. The word 'doctor' suddenly took on a whole new meaning.

Although I spent most of my time working in the hospital, I did have an opportunity to travel around northern Egypt. Wherever I went I was always welcomed with smiles and warm greetings. And, even with the little they had, the people always made generous, heartfelt offerings. They gave without expectation of anything in return. One village elder informed me that he believed that "if something could not be shared, it was not worth having at all".

One of my most memorable experiences outside of the hospital was in one of the little fishing towns I passed through - Rasheed (famous for the Rosetta stone). I had just finished visiting the town hospital and was standing outside with my camera in hand. A group of children approached me with wide curious eyes, each child pulling another behind, for moral support I suppose. I just had to take a picture of their beautiful faces and heart-warming smiles. Little did I know that this would earn me their friendship and a shadow for the rest of the trip. For the remainder of that day they followed me around, showing me their favourite play areas and hide-outs, and proudly telling their friends that I had taken their picture. By the end of the day I was famous in the town - known as the smiling camera girl.

In a country where everyday presents a new struggle, the Egyptians always took time out of their busy days to welcome me, share a smile, and belongings they may have - at the very least a cup of tea. I will not soon forget my new friends and the many lessons they taught me. Young and old, sick and healthy - each shared a gift with me; gifts of kindness, friendship and knowledge, the kind never obtained from textbooks. And yes, even the daredevil driver, I will remember him with a smile!

Special thanks to my supervisors Dr. C. Bayliss and Dr. S. Abdul Rihman.

QUICK DIAGNOSIS

Emergency Medicine Rounds

Danyal Ibrahim, MSc (9T7)

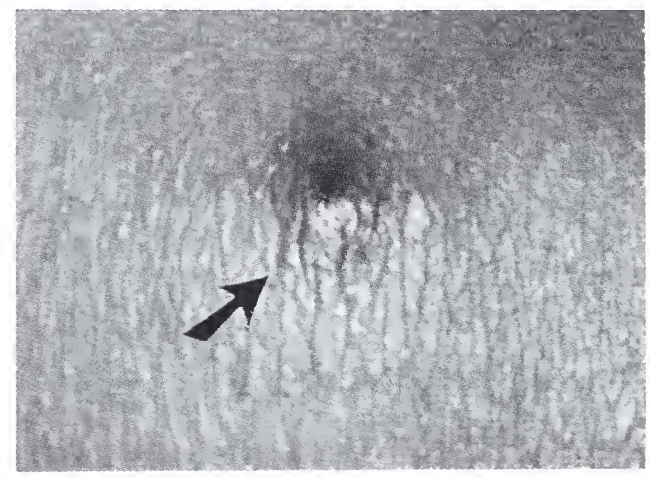
The Journal will be offering a prize of **$100** to the reader who submits the correct diagnoses for all the cases. Responses should be sent to the following address no later than **April 24, 1995.**

Quick Diagnosis Competition
c/o Danyal Ibrahim - Quick Diagnosis Editor
University of Toronto Medical Journal, Room 2141, Medical Sciences Building, Toronto, Ontario M5S 1A8

ST. MICHAEL'S EMERGENCY ROOM

Derek Jones, MD, FRCP

Case 1



A 28 year old female presents to the Emergency Department with a rash and fever. A photograph of the rash on her forearm is shown.

What is the most likely diagnosis?

Case 2

You get a STAT call from the x-ray technician that the patient you sent to the X-ray Department is now in severe respiratory distress. Chest examination reveals markedly depressed breath sounds on the right side. The chest x-ray is shown.

What is the Emergency treatment?

Case 3

A 60 year old obese male presents to the Emergency Department with recent onset of back pain and hypotension. Lumbosacral spine x-ray is done.

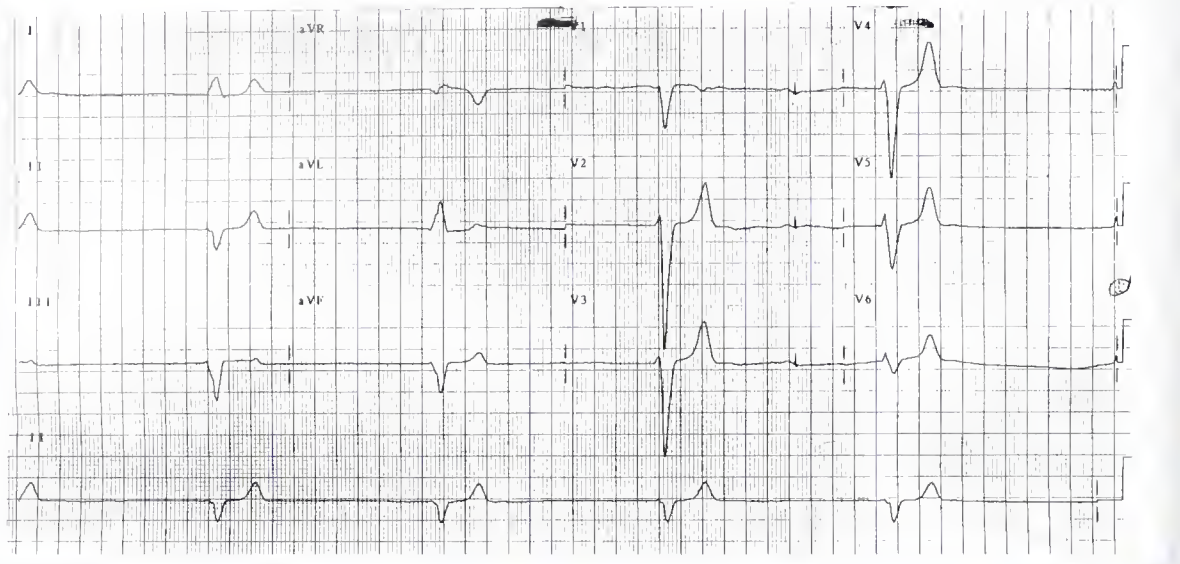
What is the single most appropriate investigation you would order to confirm the diagnosis?

Dr. Jones is an Assistant Professor in the Department of Medicine, University of Toronto and Director of Emergency Services, St. Michael's Hospital.

THE TORONTO HOSPITAL EMERGENCY ROOM

Chris Giorshev, MD, CCFP (EM)

Case 4



A 70 year old man presented to the Emergency Department with a twelve hour history of progressive generalized weakness. His long term medications included nifedipine, atenolol, furosemide, spironolactone, digoxin, glyburide, metformin, l-thyroxine and coumadin. He was placed on enalopril seven days earlier. An EKG was performed and blood was sent to the lab for electrolytes.

What is the diagnosis?

Dr. Giorshev is a Staff Physician in the Department of Emergency Medicine, The Toronto Hospital and a Lecturer, Trauma, University of Toronto.

THE WELLESLEY HOSPITAL EMERGENCY ROOM

Alan Campbell, MD, FACEP

Case 5

A 59 year old female presents to the Emergency Room with 2 days history of sore throat, raspy voice, dysphagia, and worsening odynophagia. Lateral radiograph of her neck is presented.

What is the most likely diagnosis suggested by the history and x-ray?

Dr. Campbell is Chief of Emergency Medicine, The Wellesley Hospital.

SUNNYBROOK EMERGENCY ROOM

Jessica Macrab, MD, CCFP and Barry McLellan, MD, FRCPC

Case 6

A 38 year old male complains of neck pain following a MVA where his car was struck from behind.

What is the diagnosis suggested by his neck x-ray?

Case 7

A 45 year old female unrestrained driver in a high speed head-on collision presents with closed head and chest injuries. This is her chest x-ray.

What is most concerning in this x-ray?

Case 8

Parents state that the baby accidentally rolled off the change table.

What does this x-ray suggest?

Case 9

Child with a high fever and sore throat. Neck x-ray is shown.

What is her diagnosis?

Dr. Macrab is a Final Year Resident in the Emergency Medicine Program, University of Toronto. Dr. McLellan is an Assistant Professor in the Department of Surgery, University of Toronto, Director of Trauma Program and Vice President of Team 2 Clinical Unit of Specialty Services, Sunnybrook Hospital.

SUNNYBROOK EMERGENCY ROOM

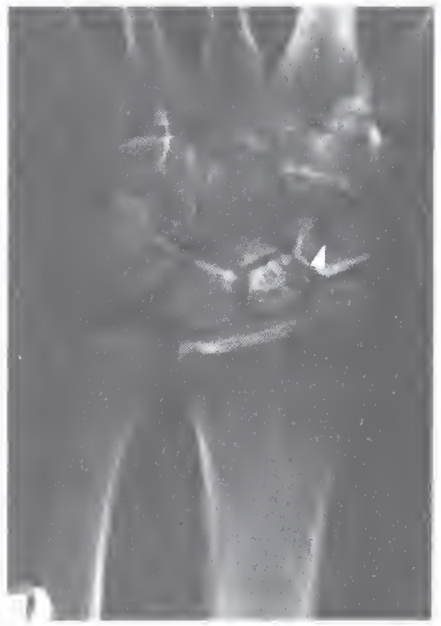
Jessica Macrab, MD, CCFP and Barry McLellan, MD, FRCPC

Case 10

A 67 year old female with severe left shoulder and arm pain and numbness.

Given this chest x-ray, what is the most likely diagnosis?

Case 11



A 28 year old male with complaint of wrist pain many months after a fall.

What is the diagnosis?

ANSWERS TO QUICK DIAGNOSIS: *(UTMJ Volume 72, Number 1, December 1994)*

Neurology and Neurosurgery Rounds

Case 1

The MRI of the cervical spine shows a cavity (syrinx) within the spinal cord. This lesion is called **Hydromyelia or Syringomyelia.** The cavitation has developed in association with obstruction at the foramen magnum due to downward herniation of the cerebellar tonsils below the level of foramen magnum, **(Chiari Type I Malformation)**.

Case 2

The diagnosis in Case 2 is **Multiple Sclerosis (MS)**. MS is a common chronic demyelinating disease of the CNS, characterized by numerous patches of demyelination (plaques) throughout the white matter. The disorder is most common in young adults and affects sensory and motor functions and is characterized by a relapsing and remitting course. The plaques exhibit a preference for the optic nerves and chiasm and uniformly localize to the paraventricular white matter of the corona radiata.

Case 3

The diagnosis in Case 3 is **Meningioma**. Meningiomas are tumours that take origin from the arachnoid cap cells and produce a globoid mass. They account for almost 20% of all primary intracranial neoplasms. The slow growth of meningiomas creates a symptomatic interval that often spans years. In this case, the tumour was in the suprasellar region, leading to visual deficits. The MRI differentiated it from a giant aneurysm.

Case 4

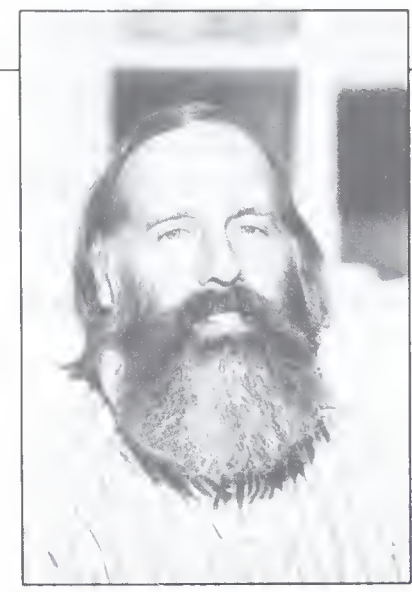
The diagnosis in Case 4 is **Cavernous Angioma,** which is composed of a honeycomb of sinusoidal channels. Cavernous angiomas are the second most frequent type of cerebrovascular malformation encountered in clinical practice. They cause seizures, or less frequently, hemorrhage. The lesions are clearly demarcated from surrounding brain tissue, and often have a multilobular or "mulberry" appearance. Cavernous angiomas are not visualized by angiography because of the small size of the vascular channels, intralesional thrombosis, and low rate flow through the malformation.

The Gairdner Foundation International Awards for 1994

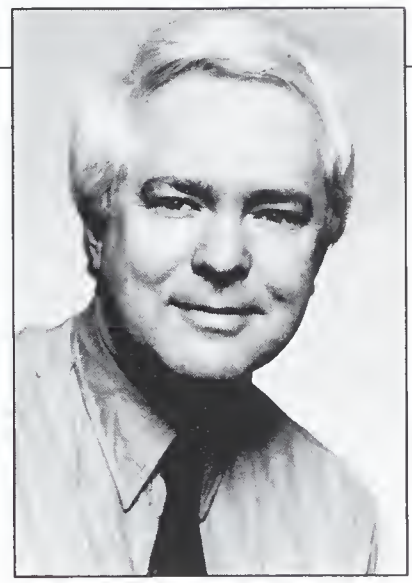
D'Arcy Little, 9T5

Dr. Pamela Bjorkman

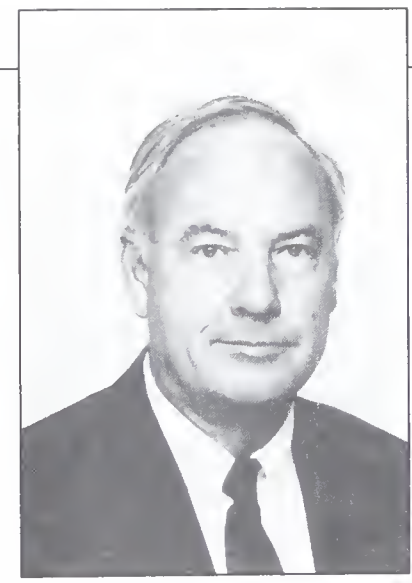
Dr. Don Wiley



Dr. Tony Hunter



Dr. Anthony Pawson



Dr. Donald Metcalf

For the third year in a row, I have the pleasure as News and Views Editor of reviewing the Gairdner Foundation International Awards that are presented in Toronto each autumn.

This year, of the five recipients, each of whom received an award of $30,000 Can. and presented a lecture summarizing their work, one was from Australia, one was from Canada, and three were from the United States. The awards were presented on Friday, October 21st, 1994 by Dr. Michael Smith, a 1993 Canadian Nobel Laureate and a 1986 Gairdner Award winner.

Dr. Pamela Bjorkman of the California Institute of Technology and Dr. Don Wiley of Harvard University were recognized for their important work on the immune system. The essential feature of the immune system is its ability to distinguish foreign proteins from normal body constituents via a specific recognition system. Foreign proteins are broken down in the body to peptides which are presented to T-lymphocytes in the context of Class I MHC proteins. In 1987, Dr. Bjorkman and Dr. Wiley, along with other collaborators, published the first description of the X-ray crystallographic structure of an

HLA protein. Co-crystallization of the HLA protein with an heterogeneous array of peptide-like material lead at this time to the realization that HLA proteins always display a spectrum of peptides on the surfaces of cells allowing T-cells to "scan" cells and to be activated when foreign proteins are presented. Although many groups have contributed to the understanding of how peptides bind to HLA proteins, the solution of the HLA structure was a turning point in the field of immunology.

Dr. Tony Hunter of the Salk Institute and Dr. Anthony Pawson of the Samuel Lunenfeld Research Institute were recognized for their contributions to the understanding of the role of tyrosine kinases in signal transduction pathways that control cell growth. The control of normal cell growth and development requires that cells can communicate precisely between each other and with the cellular environment. Dr. Hunter elucidated one of the signals that are used by all cells of the body, tyrosine phosphorylation, whereby the simple addition of a phosphate molecule to the amino acid tyrosine changes the function of the protein of which the tyrosine is a part and facilitates its interaction with other proteins in the cell. Of particular note is the fact that many of the proteins involved in regulating tyrosine phosphorylation are often mutated in cancer cells. Dr. Pawson's research illustrated the fact that cytoplasmic tyrosine kinases, involved in the induction of cancer as well as in embryogenesis and in the action of certain hormones, share common structural domains (SH2 and SH3 domains) which are involved in intracellular and intercellular protein interactions.

Finally, Dr. Donald Metcalf of the University of Melbourne was awarded a Gairdner Award for his work in the discovery and isolation of colony stimulating factors. These colony stimulating factors are the substances that stimulate the production of red and white blood cells during hematopoiesis. By studying the growth of cells in vitro, Dr. Metcalf was able to purify and characterize four specific factors, isolate the genes responsible for their production, use recombinant DNA techniques to allow the large-scale production of these factors, and institute clinical trials in vivo for the treatment of patients with depressed bone marrow function. His work has led to a revolution in molecular hematology and allowed the development of certain new forms of therapy for malignant disease.

The Gairdner Foundation was established in 1957 by the late industrialist, James A. Gairdner. The Foundation has honoured 235 scientists, many of whom have gone on to win a Nobel Prize.

We are thankful to Ms. Sally-Anne Hrica, Executive Director of the Gairdner Foundation, for much of the above information and for the photographs.

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BOOK REVIEWS

More Magic from the Medicine Man

How to Break Bad News: a guide for health care professionals

by Robert Buckman, University of Toronto Press, 1992.

and

Magic or Medicine

by Robert Buckman and Karl Sabbagh, Pan (Macmillan) 1994.

Dr. Robert Buckman

The title "multi-talented" has been devalued, for too often it is awarded to accomplished basketball players, for example, who can also swing a bat. In science and medicine admission to the exclusive club of the super-achievers has become almost impossible as specialization replaces erudition, and there are certainly commensurably fewer members today than ever before. Dr. Buckman, the oncologist, TV celebrity, academic, writer, earned the epithet long ago, and it is to his credit and our profit that he continues to challenge us with intelligent, candid books such as these.

Dr. Buckman emigrated to Canada in 1984, a fact which he mischievously conceals from his viewers on British TV channels, where he was first seen in 1977 in the company of Dr. Magnus Pyke and David Bellamy in *"Don't Ask Me"* and subsequently with Dr. Mirriam Stoppard in *"Where There's Life"*. It was as a medical student at Cambridge that "Rob" Buckman first faced an audience, performing for the Footlights Theater Company (in the wake of Alan Bennet, Jonathan Miller, Derek and Clive and many fledgling Pythons). At the peak of his medical and broadcasting successes viewers were shocked to see him evidently dying of a rare immune disease - dermatomyositis. He worked through his illness, and even incorporated it into his television series in an intensely personal way. I asked Dr. Buckman whether this encounter with bad news led him to consider the respective roles of doctor and patient. His answer was characteristically frank and engaging:

"You know, no one has ever asked me that!", (long pause, head scratch, frown), *"But I suppose I was treated pretty well.....and they did find out what it was that was killing me. But the empathy part? No, I don't think I had any special treatment just because I'm a doctor, and yet we are such bad patients. But I knew and trusted my doctors from the beginning, which is vital, and makes their life so much easier."* And the quality of the medical treatment?

"Yes, I certainly benefited. and only started to get better once a specialist drove from the other side of England to check me out. He looked me over, asked me one or two questions about my nails and put me straight on the treatment that finally worked. I don't suppose everyone can expect that kind of service."

Moving to the present, Dr. Buckman's professional experience of delivering bad news to cancer patients and their families at Sunnybrook Regional Cancer Center lies at the core of his most recent books. In *"How to Break Bad News"* he and his colleague Dr. Yvonne Kason guide us skillfully around the snares and bear traps of the most difficult of doctor-patient interactions. This book evolved from the Interviewing Skills course which the authors teach at the University of Toronto. Writing a book *"...to be read by health care professionals in all disciplines and at all levels"* is a huge challenge, exacerbated by the absence of cultural consensus on how best to help shocked and grieving patients and their families - and still less is there a body of literature on the subject. It was partly in response to requests by medical students that Dr. Buckman distilled the course into this straightforward text. As a guide, *"Breaking Bad News"* excels. The structure is logical and practical, if overly formal. Fear, pain, avoidance, denial, guilt, sympathy, humor and bargaining are introduced, and discussed in relation to the principle participants in the encounter. Virtually every aspect of the patient's, caregiver's and family's perspectives are considered in turn. Useful *"Ground Rules"* punctuate each page, offering the reader sensible advice on how to

deliver information with the minimum of pain, and the maximum honesty, compassion and support. Here are some of my favorites:

- on the fear of telling a patient that you have not the faintest idea what is wrong with them:

  "Bluffing sometimes works in exams - but usually not in real life"

- on discomfort at a patient's stress:

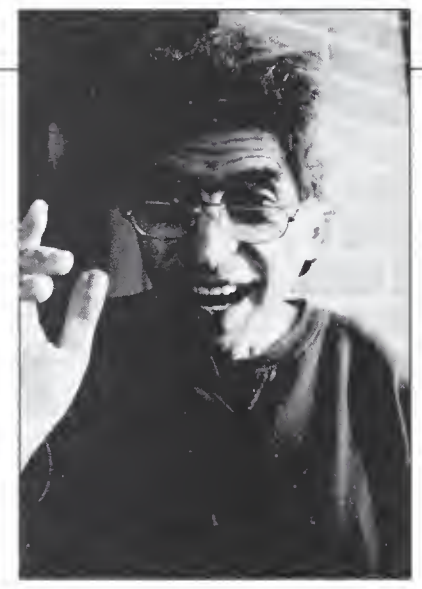
  "Premature reassurance - without acknowledgment of the patient's feelings - doesn't reassure"

- on cracking jokes with patients:

  "Respond to patients' humor - don't impose your own - a pre-emptive strike can go badly wrong"

Much of *"Breaking Bad News"* reads like good old-fashioned country doctorin', which might lead some readers to ask whether they really need to buy an instruction manual on the subject. Surely doctors are preeminent in listening to the sick and offering comfort to the dying? Evidently the millions of Canadians who consult practitioners of alternative medicine have their doubts. The phenomenal growth of acupuncture, chiropractic, homeopathy and countless other complementary, alternative or (depending on your perspective) downright flaky treatments is the subject of Dr. Buckman's latest and more satisfying book. In *"Magic or Medicine"*, written with Karl Sabbagh to accompany their Gemini-award-winning TV series, every aspect of the healer's role comes under the microscope. Beginning with Stone Age head bangers, a plausible chronology of the healing arts incorporates humoralists, vitalists, and radiologists, and all within a dozen or so pages. Sumerian sorcerers and Greek herbalists receive the same deferential treatment as our present-day techno-wizards, in language refreshingly free of condescension. Not that charlatans and cranks are spared Dr.Buckman's bile; but by reminding conventional physicians firstly of the infancy of scientific medicine, and secondly of their often lousy communication skills, useful insights are offered. That is where this book shines - in contrasting the relative skills and handicaps of both conventional and alternative treatments and their practitioners.

Those who open the book looking for an answer to the question *"Well now, does Buckman believe in all this mumbo jumbo?"* will be disappointed. Sure, he doesn't prevaricate, and his opinions are plain to see; but that's not the point. It is far more useful to ask why so many millions of regular Canadians believe in it. In fact, the irrelevance and absolutism of the hypothetical reader's question illustrate some central distinctions between conventional and alternative philosophies of evaluation and treatment. Does *"feeling better"* qualify as a clinical outcome? Is a physically measurable improvement, or even physiological *change,* required before efficacy is established? Is it ethical for a physician to raise doubts in a patient's mind as to the value of an alternative therapy when *belief itself* is obviously needed for it to work? On the other hand, how can we neglect to challenge the validity of such treatments and still call ourselves scientists? All of these questions need to be addressed if we are to understand both the appeal of alternative medicine and the shortcomings of what has come to be called conventional medicine. The biases of many previous writers on these subjects are generally evident from their introductory chapters, and in few other areas of modern medicine are arguments so angry and positions so entrenched. In this climate the hardest task is to be even-handed. Having met this challenge, Buckman and Sabbagh throw out another to us all: do we have the courage to learn from each other what works, and to discard what does not? For physicians, that generally means spending more time listening, offering support and sympathy - skills more evident in the offices of chiropractors than in teaching hospitals. Does that mean that crystals in your window, ozone and coffee enemas, krebiozen should be covered by OHIP? Nothing of the sort, and some so-called treatments actually kill. Conversely, in order to be taken seriously by the current mainstream, practitioners of alternative medicine are challenged to either substantiate their supposedly curative interventions, acknowledge that the principle ingredients are faith and a pinch of placebo (just like many conventional cures), or refer their patients to doctors whose treatments do bear scrutiny.



Dr. Robert Buckman

"In the final analysis, we can all see quite clearly that diseases need treatment, but human beings need a healer. The healer may or may not give medication, but in virtually every situation, he or she has to give some magic as well".

Julian Harriss, 9T7

A Gentle Death

by Marilynne Seguin. Key Porter, 249 pp., $19.95, 1994.

Seventy-seven percent of Canadians in a recent poll said that physician-assisted suicide should be available to the incurably ill, and the nation is currently waiting for its government to hold a promised Parliamentary free vote on this question. However, the General Council of the Canadian Medical Association recently decided, by a close vote, to officially oppose any participation by physicians in euthanasia. Thus Marilynne Seguin's A Gentle Death touches on a publicized and divisive issue of the moment. For Ms. Seguin, the book is a culmination of almost four decades of work as a nurse, and fourteen years as a founding member of Dying with Dignity, a Canadian organization which since 1980 has offered counselling to terminally-ill patients, and lobbied for their right to assisted suicide.

Ms. Seguin began her career sharing the health-care professions' established belief in the unequivocal sanctity of life, but has since come to believe that "every competent person has the right to determine the time and circumstance of his or her own death." Although her book strongly advocates for the freedom to choose assisted suicide, and documents the history of public opinion and attempted legislation on this issue, it is also intended as a guide to the entire spectrum of choices which are possible for the dying patient.

The author's philosophy evolved through her experience caring for and counselling diverse individuals, many of whose stories form the framework of this book. For example, we meet Hans, who is quadriplegic from a diving accident which happened two weeks after he and his new wife arrived in Canada, and begs for his life-supporting treatment to be discontinued; and Ian, an AIDS patient whose stomach tumours make it painful even to drink liquid, who, with the encouragement of the author, is reunited with his mother and fulfills his wish of dying at home. Ms. Seguin's exceptional narrative talent vividly conveys the hope, love, fear, and loneliness of the patients and those around them. She uses their voices and stories persuasively in supporting her call for health-care workers to do better in helping fulfill their patients' choice of treatment.

Regarding this choice, Ms. Seguin asserts, "It is not my role to judge...My role becomes that of a friend and advocate totally committed to helping the person reach the goal he or she has chosen." She approves of the decision of an elderly woman who, even though not terminally ill, wishes to commit suicide since she feels she has accomplished all the 'business' of her life. Yet, in another case, she concludes that a man who comes to her asking for euthanasia will change his mind, because he is temporarily depressed over his friend's death. These scenarios bring to mind the question of who would decide whether a patient should be allowed euthanasia, were the process to be legalized - a problem which the book skirts.

Proposed legislation would require that a physician deem the applicant to be terminally ill, and mentally competent. Many physicians ask why they are expected to be the judges of whose life should be ended. At the same time, Ms. Seguin herself criticizes the tactics of certain physicians who are overzealous about euthanasia, or motivated by financial interest. Although she does insist that any law legalizing physician-assisted suicide should contain safeguards to prevent abuse of the decision-making process, she does not elaborate on what these measures might be.

Overall, however, A Gentle Death is very informative on the options available to those who wish to plan the manner of their death in advance. It explains the advanced health care directive or "living will," recognized officially by recent legislation in several provinces, with which a person can specify the degree of medical treatment he or she would accept or refuse. It also describes the power of attorney which provides for the delegation of health-care decisions to a chosen individual if necessary. As well, the book discusses resources available for palliative care, dying at home, and respite care for caregivers.

Ms. Seguin urges the reader to "consider preparations for the end of life long before you are likely to face it...while you are healthy, relaxed, and in an optimistic frame of mind." A Gentle Death is valuable in encouraging readers to become informed of their options with regard to planning the course of their death, and to take as active a role in this process as possible. It urges them to choose a doctor whom they feel is supportive in this endeavour. Thus, for the physician, this book is also a challenge to do better than some of the doctors portrayed, who withhold food from an elderly woman who wishes to be rehabilitated from a stroke, or who force an 88-year-old man who is in poor health to remain in the hospital intensive-care unit. It is a reminder to the professional to strive to openly discuss the subject of death with patients, and to listen carefully to their wishes.

Michael Kiang, A.B. 9T7

Instructions to Authors 1994-95

The University of Toronto Medical Journal will consider manuscripts written in English on basic and clinical medical topics, as well as medical education, medical ethics, medical jurisprudence, and the history of medicine. All manuscripts should be sent to:

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A **cover letter** signed by all authors must state that the manuscript has never been published by any other journal and is not presently under consideration for publication. It should also explain the purpose of the paper and its intended readership.

We require the original manuscript with CAMERA-READY photographs, figures, line drawings, and graphs along with three additional complete copies.

Pages of the manuscripts must be numbered and typed, double-spaced, on paper approximately 22 x 28 cm. Submissions should not exceed a maximum of 4000 words and shorter papers are preferred. The title page should include the **author's names, graduating year** (if from U of T), **degrees,** and **appointments.** To facilitate the peer review process, this information must not appear on any other part of the manuscript.

Abstract - a typed abstract of no more than 200 words must be provided on a separate page. Abbreviations and references should not appear in the abstract. A translation of the abstract into French should be included, if possible. Each reference in the text should be denoted by an Arabic superscript. The list of references must be provided on a separate page, and should follow the order in which they appear in the text. References must adhere to the following style:

Reinders FX, Chalin C, and Meier HMR. Alzheimer's disease: Understanding the patient and caregiver. UTMJ 1993; 70(2): 16-20.

For further details, see CMAJ 1985;133:443-448.

Tables - Tables should have a short title, and be numbered and referred to in the text. Column headings and descriptive matter in tables should be brief. Vertical rules should not be used.

Illustrations - Each figure should be designed to fit into an area of either one or two columns of text. Photographs and illustrations must be in black and white and of good quality. Colour will only be considered if the author or an outside sponsor is willing to pay the cost. The figures, including halftones and photographs, are to be numbered consecutively in Arabic numerals, and each one must be referred to in the text. Captions should be succinct but with sufficient detail.

Drug Names - Both non-proprietary (generic) and trade names should be provided for all drugs mentioned.

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Publication deadlines are **September 15, November 15** and **January 15.** Papers which are submitted earlier will receive greater consideration.

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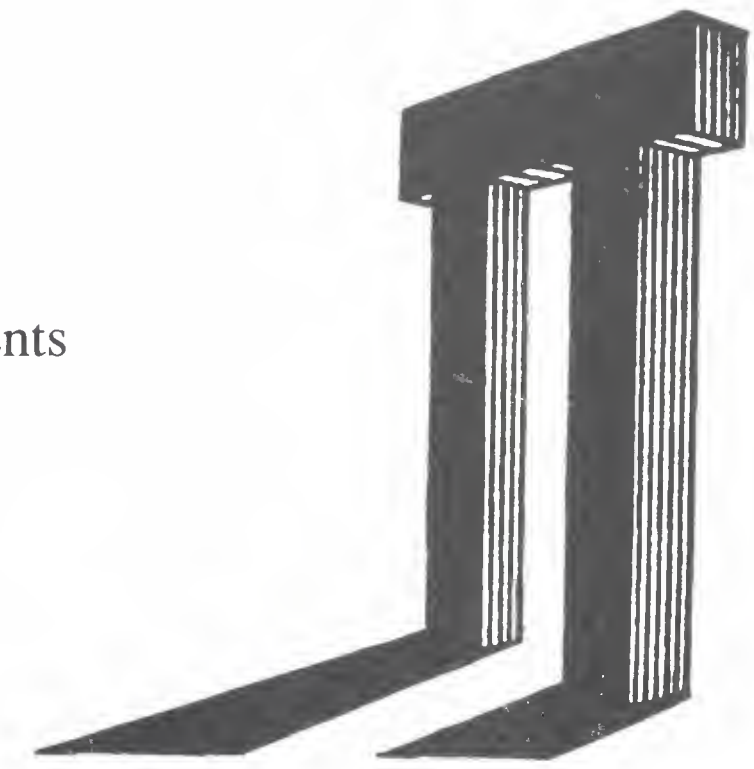

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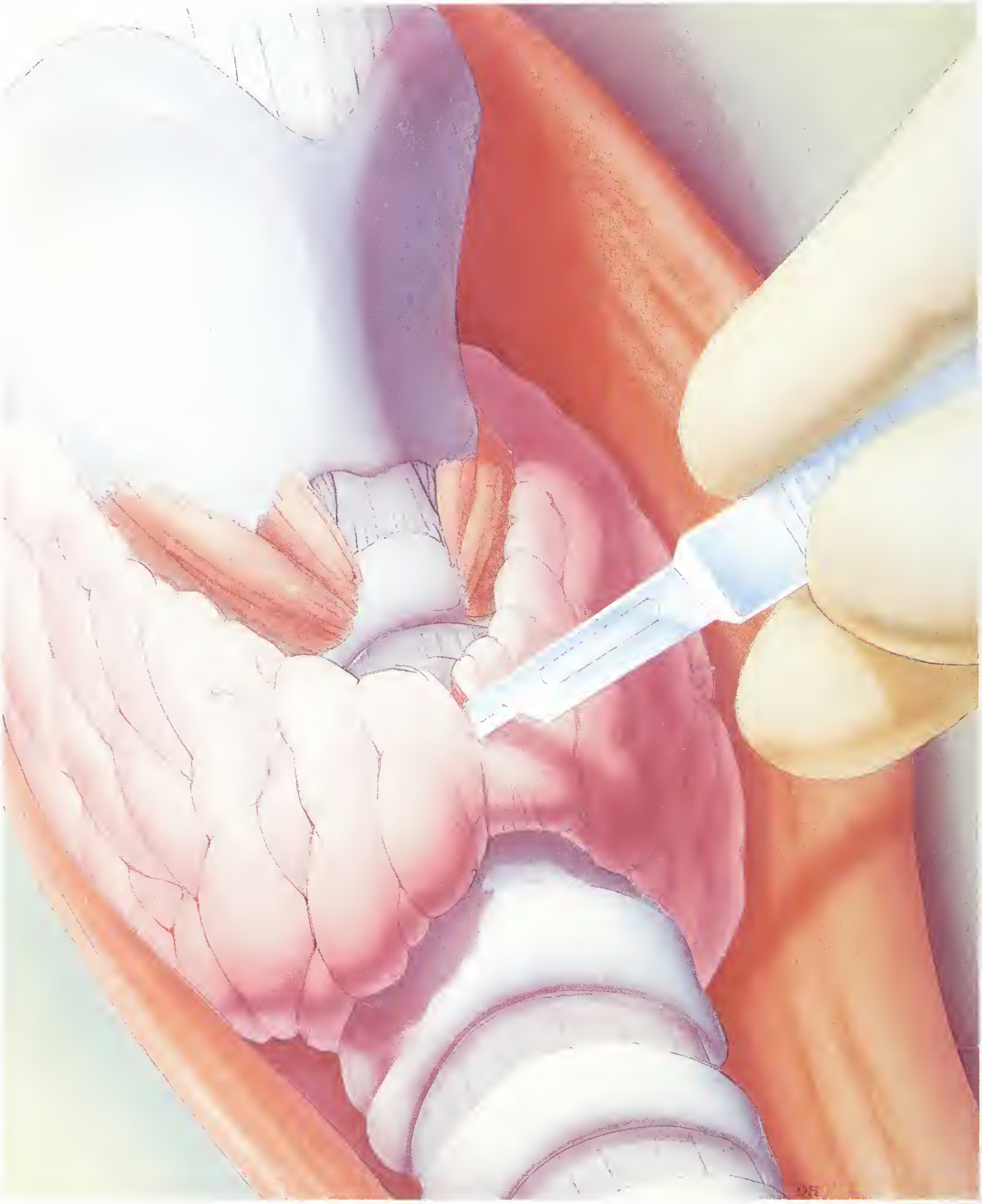

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